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ELEMENTS

OF

PHARMACOLOGY.

BY

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AUTHOR'S PREFACE.

THE following Text-Book is intended to serve as a pharmacological commentary on the Second Edition of the German Pharmacopœia. It contains in abstract only that part of the science of remedies upon which it falls to the Pharmacologist to form a judgment, and it is therefore neither a book of prescriptions nor a compendium of treatment. The latter does not concern the Pathologist, but the Physician and Clinician. The extent of and modern method of regarding Practical Medicine on the one hand, and Pharmacology on the other, do not permit the teaching of both subjects to be united in one person, on account of the danger that dilettanteism might interfere with one or other of them. Without pharmacological knowledge, the practitioner will always grope about in darkness as regards the application of remedies. To supply this knowledge is the task of the Pharmacologist. He is not, however, in a position to give directions to the Physician as to the treatment of disease; he must be contented, in formulating a science of remedies, to describe the actions of powerful agents in their practical application, more especially with respect to man, to characterise the consequences which follow the use of such means, under different conditions, for the entire organism, and from pharmacological facts to formulate general rules for the employment of remedies. Whether the actions and consequences which a remedy produces on the organism are such as will serve usefully in the treatment of a disease depends not only on the nature of the disease, but also, and more especially, on the peculiarity of the particular case. This aspect of the science of remedies, therefore, is merely part of Clinical Medicine and Therapeutics, and lies outside of the domain of Pharmacology. These principles have served as a guide in writing this work, and it should be criticised accordingly.

Many of the views developed in the following pages are based on facts which have been ascertained by a number of younger investigators working under the guidance of the Author during the last fifteen years. In friendly remembrance of their true assistance, he begs to express his warm thanks to them all.

TRANSLATOR'S PREFACE.

THE great reputation enjoyed by the Author of this work is a sufficient reason for the following translation.

Although in each section only the leading remedies belonging to the German Pharmacopœia have been mentioned, yet the list takes into consideration all of real importance, and is therefore applicable to most works of the kind.

By the kind consent of Professor SCHMIEDEBERG, various Tracings have been introduced. All of these have been executed under his personal superintendence, and are the results of original work carried out in his Laboratory at Strassburg.

To the great interest taken by him in correcting and revising the translation, as well as in bringing it up to date as regards recent investigations, I am greatly indebted.

My warm thanks are also due to Dr. GIBSON and Dr. RUSSELL for their kind assistance in various ways, and more especially for bringing the work through the press in my inevitable absence.

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ELEMENTS OF PHARMACOLOGY.

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INTRODUCTION.

Experimental Pharmacology and Therapeutics.

The term pharmacology, or therapeutics, means at the present day the science of the chemical agents which subserve therapeutic purposes. It is desirable, however, to separate the above two terms, and to give to the word *pharmacology* a wider meaning, so that it signifies *the study of the changes in general, which are caused in the living organism by chemically active substances, whether these substances be used for remedial purposes or not.*

Consequently therapeutics is only concerned with these substances which are used in the cure of disease. Many substances which cause ill consequences through their chemical action, but which find no employment as remedies—as, for example, carbonic oxide—are called poisons, and are referred to the special science of *toxicology.* Many substances belong to both these sciences, seeing that the distinction between the curative and the injurious effects of their action is only indicated by differences of degree. The list of therapeutic substances is, moreover, very variable. Many substances often disappear from the field after short use, others take their place, and in all probability meet the same fate, sooner or later. In some countries remedies are in use, the very names of which are scarcely known in others. In fact, each physician has his own set of remedies.

This state of therapeutics is due to the necessities of medical practice, but it hinders the development of scientific knowledge. For, if a substance is only to be investigated out of practical consideration of its actions, every inducement to do this disappears when the substance falls out of use. The occurrence of this should not be taken as a proof that such a substance has once for all become worthless as a remedial agent. More thorough experimental trials of it may show its use in a direction in which no one had as yet been seeking one.

Hence arises the suggestion to unite into one uniform science, for the purpose of investigation, all substances which are not foods, and which cause in the living animal body changes due to their chemical properties. This science might be called *pharmacology* or *experimental pharmacology*, seeing that it is mainly based upon experiment.

The chemical substances with which pharmacology is concerned might (simply) be called *poisons*. The popular meaning of this word would not be affected by such an extension, since there are few active substances which are not occasionally injurious to mankind.

The word *pharmaca*, which originally meant charms, and subsequently healing herbs, might quite well answer for indicating substances pharmacologically active, but it has rather an awkward sound for our present terminology.

The changes caused in the living organism by poisons may be called *poisonous* or *pharmacological actions*. Under this we must understand the abnormal alterations in the nature of the morphological, chemical, and molecular composition of the affected organs, and the alterations in their functions. That which receives the name *physiological, therapeutical, and toxicological action*, is but the result of such alterations. The latter remain the same in the physiological as well as in the pathological state of the organism, provided only that those organic structures be present upon which the poison acts. The results certainly vary under different conditions; they may be harmless, curative, or injurious.

Digitalin, for example, causes a rise of blood-pressure in the arteries, and this occurs in healthy as well as in sick persons: in the former, the minor degrees of its action have no apparent effect upon the functions of other organs, nor upon the general feeling. If, however, on the other hand, as in certain affections of the heart, the pressure in the arteries is abnormally low, causing a diminution in the secretion of the urine, and the occurrence of dropsy, it is frequently possible to remove these morbid symptoms by raising the blood-pressure through the use of digitalis; and, in consequence of this, to exercise a great influence upon the state of other organs, as well as upon the general condition of the body.

The relationship of therapeutics to experimental pharmacology is self-evident after these explanations. Like toxicology, it is a practical or applied branch of science. Pharmacology, on the other hand, forms, with physiology and pathology, a special scientific biological group.

Animal physiology has to do with life under ordinary—that is, normal—conditions; *pathology* has to do with vital phenomena which occur under unusual or abnormal conditions of very various kinds; *pharmacology* affords the knowledge of how the vital processes behave and proceed under the influence of poisons. In classifying thus, as in the case of the allied branches of knowledge, it is essentially for the purpose of dividing the labour. So far as the ultimate result is concerned, it is a matter of indifference whether, finally, pathology passes into pharmacology, or the reverse, and whether, then, both blend with physiology into a single biological science.

THE NATURE OF PHARMACOLOGICAL ACTIONS.

The changes which the organic elements undergo under the influence of pharmacological agencies are of a *chemical nature*, and often merely consist in the *transformations and decompositions* which the constituents experience, and to which they are subject under similar conditions, when the same agency acts upon them after their death. Concentrated sulphuric acid acts in the same way upon the constituents of living organs as it does upon those of dead ones. In both cases one has to do with the same destruction, only there first of all comes into consideration, in the case of the living individual, the results to the organism as a whole.

In contrast with these destructive effects, there are those in which the nature of the chemical influence, especially on the nerves and muscles, cannot be clearly determined. It is true enough that at times one can prove the presence of alterations in the condition of these structures, at any rate in a general sense—*e.g.*, coagulations of the contents of the muscular fibres and cells. Usually even that is not possible, and the poisoned cell remains apparently unaffected. That an alteration, however, has taken place, we conclude from the deviations in the functional power of the affected structures.

The integrity of the chemical composition of the organs is the one condition necessary to the normal nature of their function. Each disturbance of the latter allows us to conclude that chemical alterations of the former have taken place.

But we must not give to the term "chemical" in such cases a too narrow interpretation, and must not only include such processes as are at work between atom and atom in the modern chemical sense, but we must take into consideration, above all things, the molecular processes, as they meet us, for example, in making solutions. A solution of common salt is a molecular combination of common salt and water. Even a nerve cell or muscle cell may be considered as a molecular union of albuminous substances, lecithin, salts, water, and other constituents.

The normal state of such organic elements, more especially as regards their usual functions, is connected with a definite *molecular constitution*, which may suffer considerable disturbance through relatively slight influences. Upon these disturbances depend the deviations in their signs of activity.

This view is supported by the observation that the above-mentioned elementary structures are not only prejudiced in their function, through a slight loss of water, due to evaporation under gentle heat, or through their swelling up and losing their salts when they are treated with fresh water; but that even their death may be very easily caused to occur.

Distilled water, when taken as a drink, does not act as a poison, simply because it is changed into a harmless form immediately after its absorption, through mixing with the substances dissolved in the blood and fluids of the tissues.

The molecular constitution of the elementary organs may suffer disturbance through special substances, which are quite foreign to the organism, becoming absorbed into their interior from the outer world, and so disordering their normal molecular condition, just like a stone when it gets into the wheels of a complicated machine. Processes of this nature we are neither able in the meantime to present to our minds graphically, nor can we express them by means of a mathematical or chemical formula, nor will we, perhaps, be able to do so for a long time to come.

This kind of pharmacological action is dependent upon *the structure of the molecule of the poisonous substance.* We do not know, indeed, why the molecule of strychnine, after its absorption into the nerve cells of the spinal cord, causes that increased reflex irritability which brings about tetanus, while many other circumstances apparently quite similar have either no action or an exactly opposite one. Yet, in comparing all the poisons one with the other, we arrive at the conclusion that neither the size of a molecule,—that is, the number of atoms contained in it—nor the presence of a definite element, determines the degree of its activity. For small molecules, such as those of prussic acid, may be very poisonous, very large ones inactive, and *vice versa.* Moreover, no element is a poison in all its compounds.

We are supported in a belief in such molecular action, especially of nerve and muscle poisons, by the fact that *the organic elements are not destroyed,* but work on in a normal manner again after the excretion of the poison. Were this not the case, one dare not think of giving chloroform, for example. The action of atropine, which causes dilation of the pupil, may be kept up even weeks and months without the elementary organs concerned necessarily suffering from it afterwards.

Substances which destroy the constituents of the body cannot during life get into the interior of a nerve cell, because on their way there they cease to exist as active compounds, through the reactions which take place between them and the said constituents. Concentrated sulphuric acid, chlorine, chloride of zinc, and similar caustic substances, as such, alter only the immediate neighbourhood around the point of application, while the molecular poisons often have no effect there, and only after their diffusion in the blood and tissues do they exert an influence upon definite organs, or, as is often the case, upon only a very limited area of the nervous system.

The functional disturbances of individual organs brought about by molecular changes form, then, the *tout ensemble* of the action of such poisons. Until quite recently, it was enough simply to describe the appearances which showed themselves under the circumstances. But it is especially desirable to seek for the organs, and the parts of the organs, which are influenced by the *action*, and therefore to *localise* the latter, and describe it qualitatively and quantitatively. This is an important but relatively an easy task of experimental pharmacology. Much more difficult is it to investigate the changes which the chemical composition of the organism, its nutrition, and the metabolic processes undergo.

Only when these problems have been to a certain degree worked out, is it time to inquire whether the actions of a substance can be made use of for curative purposes.

Although pharmacology, like any other branch of knowledge, is to be pursued at first without any consideration as to practical benefit, yet there remains as the ripe fruit of such efforts the certain prospect that the results obtained will be employed for the cure of disease.

THE SOURCES OF THERAPEUTICS.

The *fountains* from which therapeutic knowledge has been drawn flow, often enough, very turbidly.

During the earliest ages of human development, the employment of curative herbs could only be a quite unconscious and *instinctive* one, just as one has the opportunity of observing occasionally amongst animals.

We often see dogs swallow stalks of grass: these, by irritating the throat and soft palate, cause retching and vomiting, and in this way remove mucus from the stomach. The mucus causes the animals to feel uncomfortable, and they therefore swallow the grass stalks.

In historical times the choice of remedies is no longer an instinctive one, but is based upon reflection in *accordance with definite principles*, but these latter, again, vary very much.

The beginnings of actual observation and experience were simple enough. If one saw sick animals recover after eating an herb, he ascribed to it curative powers, and employed it on mankind. This he did at first in every affliction, without exception; subsequently, however, only in those cases in which he thought he saw a resemblance with the ailments which had been cured in the animals. In this way *herdsmen* became the healers, as is still frequently the case.

When man did not of himself understand how to hit upon the remedy, the infallible deity had to undertake its revelation, either through signs and dreams or through the mouths of its *priests*. In consequence of this, the latter became physicians as well as priests.

The participation of a higher power in the healing of diseases lets us understand not only why material remedies recommended by the gods were made use of in order to overcome the power of the ailment by material forces, but it lets us also understand why the gods were called upon to undertake even the battle itself against disease, which was now beginning to be considered as an independent existence. At any rate the gods were expected to help and strengthen the curative powers of the remedies.

Whether the object were to recognise, or, with the help of the gods, to strengthen and properly direct the curative, and occasionally even the death-dealing powers of the bodies in nature, especially of plants, or whether it were to summon these gods, or even special spirits, directly for the destruction of the ailment, it was the custom to employ various other remedies still, and which were of a *symbolical nature*.

And so the healing art, especially therapeutics, in the very earliest ages, united itself with soothsaying, sorcery, and mysticism, and keeps up this connection among certain portions of mankind even to the present day. For, as amongst many primitive races sorcery and the healing art go regularly hand in hand, so amongst civilised people the uneducated in every land, and of every social grade we might say, do not consider it beneath them to turn to mystic treatments, often carried out under religous forms, treatments such as exorcism, laying on of the hands, &c., in order to unloose natural or supernatural powers for the healing of disease.

In course of time the *proper actions* of the remedies and their importance as a curative factor came to be known. Here we may, for example, cite the evacuation of the bowels by aperients. Such was the nature of the first scientific experience, which remained for a long time the only one.

When human thought became so far fortified that it, equipped with well-schooled logic, dared to penetrate into the deepest secrets of Nature, and into the origin of all things, without considering it necessary to make use of observation, seeing that the conceived and the actual were taken as identical, and seeing that no knowledge other than the philosophical was yet in existence, then medicine, and the main portion of it, therapeutics, passed out of the hands of the priests into those of the *philosophers.*

It was in the schools of Rhodos, Cnidos, and of Cos that, for the first time, the purely practical character of medical science showed itself, till *Hippocrates*, of the last-named school—the greatest physician of antiquity, and possibly of any age, and the most rational of all empirics—created for therapeutics, at least indirectly, a purely naturalistic manner of observation. But this standpoint was not so easy to win, for from that time dates the contest between knowledge and belief, between experience and speculation, a contest which lasted for centuries, and which, even in our time, has not been quite decided.

If we glance over the long series of centuries, a very sad picture is unrolled to our eyes. We see how the search after so-called *specifics* for separate ailments begins, and how the recommendation by a fashionable physician suffices to bring a remedy a very great reputation.

It is to be recognised as a great merit that, at the time when the sciences were being levelled away and sinking from view, any one was content to keep to the *reproduction of the Galenical doctrines*, and to the employment of Galenical remedies, as opposed to the effort to bring out, by means of the *caballah* and the *philosopher's stone*, the secret forces of Nature, even for the purpose of curing disease. Next we see how, about the time when the arts and sciences began to flourish, *Paracelsus* allowed himself to be led by signs and dreams in the recognition of the effects of medicines, or at any rate he advises one to be so; and he lays the foundation for the subsequent development of homœopathy through his reviving the Arabic doctrine of forces.

To counterpoise this state of affairs, we have little that can give us pleasure. The *introduction of numerous new remedies* from distant Oriental Asia by the Arabs, as well as the transplantation to Europe of the remedies made use of by the natives of America, are to be considered as the greatest acquisitions of this long period of time.

Consequently it must be esteemed as a very decided advance when, in the latter half of last century, physicians—the English ones more particularly—began to replace the fantastic speculations, which still thrived in Germany upon the soil of natural philosophy, by means of methodical *observation at the bedside.* This tendency has since taken root everywhere. Yet, even here, aberrations have not been avoided, for, more particularly, subjective convictions are occasionally confounded with objective experience.

From all the foregoing sources which we have touched upon has therapeutics drawn its supply, and, even now, the stamp of this origin is clearly enough to be seen; even the traces of the Galenical dynasty are still anything but effaced.

The advancing development of chemistry, of physiology, of pathology, and of other allied sciences, makes it urgently necessary to place therapeutics on a rational foundation, in order that it may not lose gradually all sympathy with those branches of study. We must consequently proceed *on definite principles,* if we wish to reach our desired goal, in the choice and application of our remedies.

The Choice of Remedies upon Rational Principles.

The processes going on in the organism, which are designated in the popular idea of the word as *sickness,* exhibit definite appearances, and a certain course and issue, which are dependent upon outside conditions. Since we are in a position, within certain limits, to alter the latter, it follows that there is a *possibility of exercising an arbitrary influence over the course and issues of the affection.* Whether the influence of an artificial interference is favourable, experience alone will teach. The latter can only be obtained when we quite clearly know what are the course and issue of disease, supposing there had been no such interference; but this we can rarely do. For whether a disease, which may just as well as not end in recovery, will take one or other course, cannot be foreseen with absolute certainty, but only with a certain degree of probability. Hence we shall often enough be more or less in doubt as to the result of any given influence it exerts, *e.g.*, as to the action of a remedy.

Experience will here usually be gained if the observer, when weighing previous accounts, or his own views, forms *an idea of the further course of the case in hand*, and in accordance with this employs what seems to him a suitable treatment. By comparison of the result of the last method of treatment with the result which he had originally expected, he can judge of the success of the remedy he has made use of. Since, however, that presumption as to the course of the disease need not by any means necessarily be correct, it follows as a matter of course that it depends, more or less, upon the observer's own idea what success he is inclined to ascribe to the remedy employed, and to what extent he makes the cure attained dependent upon the treatment. And, consequently, the knowledge gained by this *subjective valuation method* is an exceedingly uncertain one, against which the one will proceed to wage war with critical pains, while the other speaks with pride from his positive position.

Propositions thus won by careful valuation may multiply in course of time, and, as they increase, point so steadily in the same direction that they at times attain the value of facts. Yet in these cases even an ultimate mistake is not impossible, as seems to be the case, in the present day, with the universally and long praised success of the treatment of poverty of blood by iron.

Greater safety is expected from a *statistical method.*

If we know the general course of an illness in an average of a considerable number of cases, and compare this number with another correspondingly great, in which all were subjected individually to the same treatment, we would be able to judge with certainty of the average influence of this treatment; and the certainty increases generally with the number of observed cases.

However, almost insuperable *difficulties* oppose the carrying out of this method. The cases in both series must not only be as far as possible similar, but the treatment—that is, the remedy employed—the influence of which upon the course of disease we are to prove, must not be subject to too great variations in its nature and strength ; more particularly, it must not be used at the same time as other ever-varying methods of treatment. But even when we succeed in overcoming these difficulties and obtaining correct results, the latter can only claim a purely general importance ; and we dare not apply them to individual cases, because each of the latter has its own course and issue, which we cannot foretell beforehand.

These purely empirical methods give us no insight into the processes which are at work when a disease is being treated with medicines. The *rational method* aims at opposing the changes brought about in the individual organs through the disease by means of artificially induced changes, which either influence the course of the disease in a favourable direction, or remove those occurrences which are hurtful to the organism as a whole and worrying to the individual.

The morbid changes in the functions of the organs can only be quantitative in their nature. The dangers to the whole body are due to the fact that the function at one time is excessive, at another time too deficient in action. The duty of rational therapeutics under such circumstances is to lower the activity when too great, and raise it when too low. Should the function of the affected organ consist in its carrying on excretion or nutrition, the variations of which control the nature of the ailment, the latter can be attacked by seeking to strengthen or moderate those processes—that is to say, the functions. If such a method of attack be not possible, we must merely content ourselves with rendering the result of these disturbances as harmless as possible.

If, therefore, we wish to treat a disease with medicines, it is presupposed that first of all we have an exact knowledge of its nature. The situation of the pathological changes and their influence upon the various organic regions must be known, and the dependence of the individual morbid appearances upon one another, and upon the pathological lesion, be perfectly clear. Finally, for such a method of treatment a thorough knowledge is necessary, not only of the actions of the customary remedies, but also of those of the pharmacological agents in general.

The *pharmacologist* investigates these actions in the only way left open,—that is, the experimental. *The clinical physician* uses them in the way adapted to his purpose. Since, however, the whole matter depends not only upon the action itself, but also upon the suitable degree of it, the duration and frequency of administration necessary, and occasionally upon a judicious combination of various remedies, which must all, moreover, not infrequently be properly balanced with each other; so then, because of these conditions, actual experience and practice step forward here with their just claims as a medical art. Science and practice go hand in hand. We can only speak of them opposing each other when the latter remains on the lowest step of empiricism.

THE CLASSIFICATION OF PHARMACOLOGICAL SUBSTANCES AND OF REMEDIES.

The numerous substances with which pharmacology has to do, and with which it will have to do still more in time to come, necessitate a *systematic classification*, by which a ready oversight and well-planned method of procedure in the investigation of their actions can be possible.

A *classification based upon purely chemical principles*, or upon the action upon individual organs, is objectionable, because it is usual enough for only those characters to be taken notice of which are chosen arbitrarily out of many others present, or which have no connection at all with the pharmacological nature of the substances.

For a pharmacological system, those *chemical properties* are to be taken into account which share in causing the actions upon the living body, while others, which are particularly characteristic and important, as regards the purely scientific consideration of the bodies, from a pharmacological point of view, often offer no special interest. A chemical system is therefore not at the same time a pharmacological one. We know that Mannite and Glauber's salts, which are chemically as widely separated as possible, act as aperients, because of their having certain properties in common: hence, in a pharmacological scheme, they must be placed alongside of each other.

A *classification according to the action of the substances* on individually important organs, likewise only takes notice of special and more striking points in a very one-sided manner. It is rare to find that a poison attacks only one organ; usually several are acted upon at one time. The designation brain poison, cardiac poison, &c., does not indicate the nature of the action, nor does it comprehend the behaviour of the substances in question, towards the rest of the organs.

Hence in setting up a pharmacological system, one will have to proceed in the same way as a botanist when he is grouping plants into natural families; and accordingly he must note all those leading characters of the active substances, which from a pharmacological point of view are of importance; those substances whose properties and actions most agree with each other can, therefore, be united into *pharmacological groups after Buchheim's* plan, and each of these can be named after one of the best known of the substances in the group.

The Strychnine Group includes, according to this classification, all those poisons which stand as near as possible alongside of that alkaloid, as regards their actions and general behaviour in the body. *To the group of Glauber's Salts* belong all chemical compounds which, after suitable doses, and without causing any other noticeable effects, evoke fluid stools, through the fact that they are not easily absorbed in the bowels.

In this way *Buchheim* succeeded in setting up a *natural system*, which answers the claim that, as the development of pharmacological knowledge advances, it can always be made more and more perfect without altering the basis. Each group can be gradually more and more sharply defined, newly formed ones arranged alongside of the old ones, and the whole of them, if need be, rearranged, without the system itself needing to be given up or replaced by another, as is inevitable with an artificial system. Investigations which are carried on without any consideration for some system of this sort will very soon be of no value.

The present imperfection of Buchheim's system depends essentially upon the simple fact that we do not know even the active principles of many drugs and raw materials, to say nothing of the action of these principles, and their behaviour in the organism.

It is impossible, however, to set up *any special system* of *therapeutics*, seeing that it deals with the practical utilisation of certain actions of the individual substances. Yet we are justified in associating remedies according to those of their actions which more or less exclusively come into consideration in the treatment of disease, but this must be founded upon their pharmacological grouping. Hence we may speak of aperients, but we dare not throw all the different groups, *e.g.*, Glauber's Salts and Senna, into one; for the peculiarity of each group often affords a special indication for its employment.

CHAPTER I.

NERVE AND MUSCLE POISONS.

Many substances, after their absorption into the blood and tissues, cause *functional disturbances in various regions of the nervous system and of the muscles.* Simultaneous actions at the point of application, and at the seats of the nutritive processes, are certainly not excluded, but take a comparatively subordinate place. For example, alcohol, when concentrated, causes an inflammatory irritation, which becomes weaker in proportion as water is added. Yet the action of alcohol upon the nervous system is independent of the concentration and its relationship to the point of application, and always exerts its influence in one and the same way, provided enough be absorbed.

With other substances, such as the metallic compounds, the action upon the muscles and nerves plays a subordinate part in comparison with the local caustic action and the disturbances in the nutritive area.

If the quality of the specific sensations be left out of consideration, then the changes in the nervous functions can be merely quantitative; hence the poisons cause either an increase or a decrease of the normal irritability, or a direct irritation of the nervous system. The falling off or destruction of the irritability, and the weakening or suppression thus caused to the function of the nerve and muscle tracts affected, go by the name of paralysis. Under this term is also understood the motionlessness of whole organs—*e.g.*, of the heart and limbs—as well as of the whole individual.

Increase of function may be due to one or two causes: either the *irritability* is increased while the strength of the *stimuli* remains the same, or the latter have increased while the former remains as it was. In both cases, and these can occur simultaneously, the effect is the same, that is, there is an increased *irritation* and a greater *functional activity.* In reality, we meet almost only with the latter, and are not able to refer the cause to either the one process or the other. At times, however, we can do this more or less approximately.

The changes of function undergone by the *muscles* under the influence of poisons are not so simple, for in their case, in addition to the irritability, we have to take into consideration the working power and the conditions of elasticity. No general rules can be deduced as yet from the experiments made hitherto.

Amongst the nervous elements only the central and peripheral *end-organs* are touched by the poison. The *conducting fibres*, on the other hand, remain intact till the death of the organism. At any rate no certain case is known in which the conduction of the stimulus along the medullated nerve fibres has been interrupted during life.

When reference is made to the action of the poison upon definite *centres* in the brain and other parts of the nervous system, then only the *central* end-organs are to be understood, without any reference to their anatomical position. It is certain that there are centres of sensation, even though they cannot be localised within exactly determined areas of the cerebral cortex.

The Strychnine Group.

To this group belong, besides *strychnine*, various other alkaloids, especially *calabarine*, *akazgine*, *brucine*, and *thebaine*, which at present, however, are of no importance in therapeutics. Common to all is the typical strychnine action. Brucine and thebaine cause in frogs, even before the access of the tetanus, a more or less pronounced paralysis of the brain functions, and possibly also of those independent functions of the spinal cord which are not reflex in nature. In consequence of these actions, they form the transition between the strychnine and morphine groups.

The characteristic symptom of the action of strychnine is the *tetanus*, which consists in tonic contraction of all the voluntary muscles—a contraction which generally comes on suddenly, and lasts from a few seconds to many minutes. The short intermissions, which often follow upon each other with the rapidity of lightning, are interrupted by somewhat longer lasting remissions. In the most severe forms of tetanus these interruptions are wanting, and the whole body appears as rigid, immoveable, and hard as a board.

Since, when the muscles of the vertebrata contract, the action of the extensors overcomes that of the flexors, tetanus causes a stretching of the trunk (orthotonus) and of the limbs; the former may even be bent far backwards (opisthotonus).

The *cause of tetanus* is an excessively increased reflex irritability of the spinal cord, of the medulla oblongata, and of the brain. When the latter organs are in this state, the spasms get excited by the slightest, often imperceptible, stimuli which may meet the eye, the ear, and particularly the organs of touch, so that they apparently come on without a cause. Nevertheless, in the mildest degrees of the action of strychnine, that is, after a dose of $\frac{1}{50}$–$\frac{1}{100}$ mg. (= $\frac{1}{3000}$–$\frac{1}{6000}$ grain) to a frog, the attacks will come on only after perceptible external stimulation. This proves that tetanus is a reflex spasm.

In *men* we often cannot induce, by means of strychnine, any striking increase of reflex irritability without at the same time tetanic symptoms showing themselves. On the other hand there often occur, after somewhat large medicinal doses, frequent twitchings and stiffness, especially in the muscles of the neck and lower jaw, sensitiveness to sensory impressions, trembling of the limbs, and difficulty of breathing.

After prolonged use, doses which, given by themselves, have no perceptible effect, often cause a condition of increased reflex irritability which is not so great that in a healthy person the reflex movements become uncontrollable. But if, after apoplectic attacks, the *paralysed limbs* be no longer under the reflex inhibiting power of the will, then, in consequence of this action of strychnine, they not infrequently fall into a state of active movement, or even of tetanic rigidity. These appearances, which are to be seen after sensory stimuli in paralysis of the spinal cord, even without the employment of strychnine (Brown-Sequard), can hardly have the importance of moderate passive movement from a therapeutic point of view. In paralytic conditions no other result is to be expected from the usually imperceptible increase of reflex irritability brought about by the strychnine.

Moreover, strychnine increases the irritability of the *centres for the automatic* functions of the central nervous system, and sets them in a state of increased activity. This is to the greatest extent the case with the origins of the *vascular nerves* and the *cardiac inhibitory fibres* of the vagus. In consequence of this, the blood-pressure of curarized animals rises, while the frequency of the pulse becomes simultaneously slowed (S. Mayer). In frogs the *muscular tonus*, which has its centre in the spinal cord, experiences in like manner an increase.

The observation, made many years ago, that in amblyopic and amaurotic states an *improvement of the visual power* is brought about by strychnine, has acquired special notice through the therapeutic experiments of Nagel. Even in the case of a healthy eye, after doses of two to four mg. ($\frac{1}{30}$—$\frac{1}{15}$ grain) an increase *in the visual acuteness* can be achieved, especially at the periphery of the field of vision, along with a widening of the latter, and this takes place only in that eye in the neighbourhood of which the strychnine is subcutaneously injected (v. Hippel). The latter circumstance, as well as the long duration of the effect, which lasts indeed for days, points to a local influence of the poison upon the retina. Yet, to start with, it is more probable that an increase of the irritability of the centres in the brain for the perception of light is the cause of the increased visual acuteness, seeing that an equal stimulus by light will cause, under these conditions, a stronger sensation than before. Although after the use of strychnine the increase of visual power in atrophy of the nerve lasts a considerable time, at any rate in some cases, yet a cure, properly so called, of this affection cannot be expected.

After the internal use of 0·02 g. ($\frac{1}{3}$ grain) of strychnine, the *sense of smell becomes extraordinarily increased*, and in consequence of this, ill-smelling substances, such as asafœtida, garlic, and valerian, cause a pleasant impression (Fröhlich). Upon the *sense of taste* the poison seems to have only a slight effect (Lichtenfels, v. Hippel).

The use of nux vomica and strychnine, which was at one time the practice, *in all sorts of diseases*, especially of the nervous system, has at present almost quite gone out of fashion. It is only in cases of *motor paralysis*, due to various causes, that this remedy is tried again and again, although the reports of favourable results are very few. The action in these cases can only consist in the fact that irritability of the motor centres, though otherwise intact, has been lessened in consequence of illness, and that it gets raised transiently under the influence of the alkaloid. Whether or not by means of this the return of the affected parts to their normal condition will be assisted, we cannot say beforehand.

Upon the *heart*, the *muscles*, and the *peripheral nerves*, the alkaloid has no direct action whatever. The *cause of death* after poisoning by strychnine is to be found in the general exhaustion of the nervous system, and, to judge from experiments upon animals, it seems that an important part is played here by paralysis following stimulation of the nervous centres for the vessels. *The average fatal dose* of strychnine for a grown-up man amounts, for internal administration, to 0·10 or 0·12 g. (= $1\frac{1}{2}$ – $1\frac{3}{4}$ grains). There are, however, cases in which death has occurred from 0·03 g. (= $\frac{1}{2}$ grain), while in other cases recovery has occurred after 0·6 (= 9 grains) or even 1·25 g. (= 19 grains). In these cases it is to be remembered, however, that emetics had been given.

A toleration of strychnine does not seem to occur, but to a certain degree the opposite, because the increase of irritability of the nervous system, when it has once come on, lasts some time. Thus a cumulative action readily takes place under the continued use of the remedy.

The extract of nux vomica, in which strychnine and brucine are the only active principles, is frequently employed, and apparently with good result, in *chronic catarrhs of the stomach and intestine*, the aim being to suppress certain symptoms, more particularly disturbances of the digestion, unpleasant sensations in the neighbourhood of the stomach, and diarrhœa. Whether strychnine plays here only the part of a bitter substance, or whether it influences in its own way the innervation of the digestive organs, has not up till now been decided.

Instead of the extract, the accessory constituents of which evidently retard the absorption of the alkaloid, and favour its passage into the intestine, we could employ in a mucilaginous emulsion the *tannate of strychnine*, which is insoluble, and is therefore very slowly absorbed. In this way we could attain an exact dosage, which is an impossibility with the extract.

THE CURARINE GROUP.

Curarine is an amorphous alkaloid, still but little known, very soluble in water, and obtained from certain species of strychnos (Baillon), which yield the South American arrow poison called curara. One kind of the latter contains about 4 per cent. of curarine (Buntzen), according to hitherto unpublished investigations.

The poison paralyses *the ends of the motor nerves* of all the voluntary muscles, without at first affecting other organs.

Doses of 0·005 – 0·010 mg. ($\frac{1}{12}$ – $\frac{1}{6}$ grain) of picrate of curarine, or of a corresponding quantity of curara, render *frogs* perfectly motionless, yet the heart continues to beat firmly and the muscles retain their irritability. In this condition the animal can remain eight to ten days, till perfect recovery occurs, after the passage of the curarine into the urine (Bidder).

In *mammals* the excretion of the poison by the kidneys takes place so rapidly, that the absorption by the stomach does not keep pace with the elimination. Consequently far greater doses of curara are harmless when taken internally than are enough to cause death when injected into the blood or under the skin. Schomburgk, during his travels in South America, took very large quantities without harm for swamp fever. If, however, comparatively large quantities are brought into the stomach (Fontana), or the excretion of the alkaloid is prevented by tying the renal vessels, the symptoms of poisoning occur after this method of administration just as quickly as after its injection under the skin (C. Bernard).

Moreover, in the case of mammals, curarine paralyses only the *ends of the motor nerves*, without at first causing any other evident effects. The animals die, when left to themselves, through the effects of the cessation of the respiratory movements. If the latter be replaced artificially, by blowing air into the lungs, the perfectly motionless animal remains often many hours alive. The heart pulsates all this time with undiminished vigour, and keeps up an almost normal blood-pressure in the vascular system, which is little affected by the poison.

When curara is used in the treatment of disease, no action comes into consideration beyond the paralysis of the ends of the motor nerves. In curarized animals which are under artificial respiration, strychnine does not cause tetanus, because the transmission of the excessive stimulation from the central nervous system to the muscles is prevented. After the excretion of the two poisons perfect recovery occasionally occurs (Richter). In men neither tetanus nor any other form of spasmodic affection can be treated in this way, because, if we wish to achieve a certain result, an almost perfect paralysis of the nerve ends is requisite, and this cannot be achieved without efficient artificial respiration. The latter cannot be kept up in animals, far less in men, for any length of time, without the greatest danger; for through the blowing in of the air the thorax is expanded by the forcibly dilated lung, and consequently the latter is injured.

One essential cause of death, in severe and prolonged cases of strychnine tetanus, cannot be removed by the use of curara, judging from experiments in animals—viz., the *paralysis of the vasomotor centres*, as described under the strychnine group, which follows the original state of irritation, even though the accesssion of tetanus be prevented by curara and artificial respiration. The sinking of the blood-pressure inevitably brings about a fatal issue.

Attempts have been made to treat *tetanus*, and other forms of spasm, *by means of doses of curara*, so small as to have no evident effect. If in such cases a cure resulted, it certainly had no connection with the remedy employed.

In spite of the unfavourable prospects which present themselves, according to the foregoing explanations, as regards the application of the action of curara to the treatment of those affections in general, *a successful application of this remedy in certain cases of tetanus* is by no means excluded. It is conceivable that the latter only just oversteps in intensity and duration that boundary on the further side of which the fatal cases begin. It is in such a case that we would most easily succeed in maintaining life till danger was past. Even a moderate but quite distinctly pronounced curarine action is able to break the violence of the spasms. The stoppage of the breathing can be easily set aside by means of simple artificial manual respiration. In this way Offenberg succeeded in effecting a cure in the special form of tetanus called rabies.

Curara has wisely not been taken into the pharmacopœia, because it is impossible in commerce to get preparations of approximately uniform strength. *Hence before use the strength of its action must be tried upon frogs.* If 0·1 mg. ($=\frac{1}{600}$ grain) of a given kind of curara causes rapid paralysis of the animal, then we can inject in the form of a filtered five-per-cent. watery solution 0·02 g. ($\frac{1}{3}$ minim) subcutaneously at first every quarter of an hour, then every half hour, and afterwards at still greater intervals, till distinct signs of paralysis come on. According to experiments made on animals, the respiratory movements are still fairly energetic after poisoning with curara, even though the voluntary movements have been to a very great degree lessened. A moderate amount of artificial respiration will readily remove any threatening danger.

Many *ammonium bases* cause, along with other actions, a paralysis of the ends of the motor nerves, just as curara does. Whether one or other can replace curara, further investigations alone can show.

THE MORPHINE GROUP.

Morphine paralyses in a peculiar way the functions of the cerebrum, an action which goes by the name of *narcosis*, and causes, as strychnine does, an *increase of the reflex irritability* of the central nervous system, which culminates in tetanus. Of the remaining alkaloids of opium, narcotine, codeine, and papaverine act similarly, only the narcotic action, even in the case of codeine, is, in comparison with the tetanic action, much weaker than it is in the case of morphine. *Thebaine* belongs to the strychnine group, as above stated (p. 14). *Narceine* is quite inactive.

The characteristic *tetanus of morphium* comes on with perfect regularity only in the case of the lower animals, *e.g.*, frogs. In the case of certain races of mammals, especially cats—less often in the case of dogs—it is to be seen perfectly pronounced. On the other hand, a very decided degree of increase of reflex irritability is never absent, even in the case of the latter race of animals. In some cases tetanus has also been seen to occur occasionally in severe cases of poisoning in human beings.

This relative *immunity of the more highly organised creatures, as regards the tetanizing influence* of morphine, is to be explained by the fact that in them death supervenes in consequence of the paralysis of the brain, before that degree of increased reflex irritability comes on, in which a pronounced tetanus breaks out. Even frogs become perfectly motionless before the spasms break out.

In man the actions of morphine and opium are identical, because the remaining alkaloids, which evoke spasms more strongly than morphine, especially the substance thebaine, which belongs to the strychnine group, are only contained in the drug in small amount.

The action of morphine upon the *brain* is in the case of every mammal essentially the same. Variations in different classes of animals can be referred to the unequal importance of the functional activity, and to their varying nature in this organ.

In *frogs* the functions of the great brain, middle brain (corpora quadrigemina), and cerebellum are put out of action one after the other, just as when we slice away these parts successively; but there is this difference, that in the latter case the function of the part removed at once entirely ceases, while in the case of poisoning a relic may still survive of the functions of one part, as, for example, of the great brain, even though the functions of the neighbouring area, the middle brain, have begun to be attacked. We must consider as dependent on such an action those *symptoms* which develop in frogs after 0·02 to 0·05 g. ($\frac{1}{3}$–$\frac{3}{4}$ grain) of morphine in the course of a few hours. They consist at first in the loss of the power of voluntary movement, though at the same time the latter occurs quite co-ordinately after artificial external stimuli. Then come on disturbances of co-ordination and equilibrium (action on the corpora quadrigemina), and after a time the animal can no longer make a spring, though it is able to recover the squatting position after being laid on its back (corresponding to the removal of the cerebellum). At last perfect immobility results, which is not disturbed by external stimuli even in the form of reflexes. Only when the animal has fallen into this state does the increased reflex irritability begin which ends in tetanus; it occurs as a rule more rarely, and only after large doses before the supervention of the loss of motion.

In the *case of higher animals and of man*, first of all the susceptibility to strong sensory stimuli is lowered, especially for such as excite pain and coughing, but the sensation of touch remains at first intact. The pain-soothing action creeps on without the sensorium necessarily losing its activity, as shown by the access of sleep, but the inclination to the latter soon becomes noticeable. This points to the fact that, to start with, the irritability of the different areas is lessened, and the susceptibility for all external stimuli blunted. No states of stimulation can as a rule be proved to be present in any given area of the brain, and it is only in certain cases that the ideas get disordered, not only immediately before the access of sleep, but while the patient is quite awake. The ideas then become more lively, fleeting, and come on unsuggested, as the mood varies and the power of thinking becomes impeded.

These symptoms have been ascribed to a *directly stimulant action of morphine and of opium* upon the sections of the brain concerned therein. Even from the very inconstancy of these symptoms one must accept the opinion, expressed so early as last century by J. Johnstone, that this excitement is merely due to the narcotic action of morphine and opium. It is evidently merely a matter of the disturbance and of the alteration of the equilibrium of the separate functions of the brain. The area for ideation is evidently quite intact when sensory stimuli are already beginning to lose their effect. The former thus has less stimulation and guidance from outside, and starts forthwith of its own account into action, just as occurs before one falls fast asleep. Somewhat later it, too, becomes directly influenced in the sense of being paralysed, and then the excitement is allayed.

If this degree of action is reached, *sleep* is certain to come on, provided external stimuli be not used intentionally with a certain intensity, for they still preserve their effect because of the continuance of the reflex irritability. Passive and active movements of the body, and rapidly varying energetic stimulation of the senses, usually prevent the occurrence of sleep, or indeed of deep narcosis. As the action advances, the irritability of the brain dies out gradually, and a deep and inevitable sleep comes on, then unconsciousness proper, and finally deep coma. After this the paralysis gradually attacks the medulla oblongata, and first of all exerts its influence upon the *respiration*, which becomes slower, irregular, intermittent, and stertorous, till it finally comes to a stop. The cessation of the respiratory movements is the *cause of death* in acute poisoning with opium and morphine. In rabbits the respiration presents an appearance which is exactly like the *Cheyne-Stokes* phenomenon (Filehne).

The condition of the vessels deserves special attention. In animals the tonus of the vessels, in consequence of paralysis of the origins of their nerves, is only in the most severe cases of poisoning so far affected as to cause a lowering of the arterial blood-pressure. In man, on the other hand, a *dilatation of the blood-vessels of the skin of the body and face is often* to be observed after medicinal doses. The nervous centres for the vessels of these areas are exceedingly open to all influences, especially those which bring about a loss of tonus.

With this action upon the vessels we must probably associate certain *appearances* which we have the opportunity of observing in cases of poisoning. To these belong the feeling of warmth and the reddening of the face, the outbreak of perspiration, eruptions in the form of pimples, and itchiness of the skin. A local action of the alkaloid upon the walls of the small arteries we have no reason for believing in. The preliminary redness gives way afterwards to pallor, if the rest of the vessels have dilated from the poisoning proceeding further. Since the dilatation of the vessels of the skin forms only one of the conditions for the occurrence, we can easily understand why we often miss it.

We cannot distinctly decide from the facts which we have at hand whether the *vessels of the brain* likewise become early dilated, and whether this circumstance forbids the use of morphine in those ailments and states in which a *tendency to congestion of the head* is to be found—as, for instance, is alleged to be the case in childhood—yet such a view has a certain amount of likelihood.

The *contraction of the pupil* is frequently, but by no means always, seen in man, in the more advanced stages of the action of morphine; it does not occur when morphine is instilled into the eye directly, and is only of diagnostic value. It cannot be associated with the direct paralysis or irritation of special parts of the brain, but is probably dependent upon more complicated processes.

Morphinism and chronic morphine poisoning, which are clinically so very interesting, belong to the subject of toxicology.

Of the peripheral organs, only a few are affected directly by the action of morphine; more particularly the *muscles and peripheral nerves* remain quite intact. That the *nerves of touch* do not lose their irritability, even in the most severe degrees of morphine poisoning, follows directly from the fact that in animals every touch or shake induces twitchings and reflex spasms; and just as little do we find a diminution of the local sensitiveness *to pathological stimuli*, such as are caused by the secondary coil of an induction apparatus (Jolly and Hilsmann). It is only when the nerve of the amputated leg of a frog is dipped into a watery solution of opium or morphia that it loses its irritability (Joh. Müller). That has, however, no influence whatsoever upon an estimate of the state of matters during life.

The functions of the *heart* are not directly influenced to any appreciable extent, yet towards the end of a fatal case of poisoning a paralytic state of the automatic motor cardiac ganglia (cardiac narcosis) may contribute, along with the dilatation of the vessels, to the fall of blood-pressure. This is just what one sees in a much more pronounced degree in cases of poisoning with prussic acid, and with the substances of the chloroform group.

The *movements of the intestine* are much more strikingly influenced by morphine. In consequence of lessened peristalsis, there comes on in healthy individuals after the use of morphine and opium a retardation of the motions, and even constipation. In cases of *diarrhœa*, such as occur in acute cases of intestinal catarrh more particularly, the violent peristalsis is checked, the evacuations also cease, and the morbid mucous membrane finds in the quiet thus obtained the conditions for its cure.

The *rationale of this action upon the intestine* has not yet been satisfactorily explained. Paralysis of the motor ganglia and of the muscles has certainly nothing to do with it, and just as little can we believe seriously in the strengthening of the inhibitory influence of the splanchnic. Hence the most probable view of all is, that certain nervous elements exist in the wall of the intestine, and that these receive centripetal (sensory) stimuli, and transfer these to the motor centres, and that the irritability of these "*reflex-helping*" nerves becomes diminished (Nasse). With this view harmonises the fact that chemical irritation of the poisoned intestine with a crystal of common salt causes only a local contraction, but not an undulatory propagation of the latter, as in the healthy intestine (Nothnagel).

Opium and morphine are used very generally for the suppression of immoderate movements and contractions of the intestine. They play their most important parts in the treatment of acute *intestinal catarrhs*, but while in these cases the evacuations are to be moderated, we seek, on the other hand, to arrest the continuous constipation of *lead colic* by one or other of these preparations. Here the success is due to the fact that the spasms of the intestinal canal brought about by the lead poisoning, and kept up by sensory irritations, are removed, and so the intestine is opened again for the passage of the fæces.

In the treatment of intestinal affections opium is preferred to morphine; whatever justification there is for this, must evidently be found in the same kind of relationship which we find existing between extract of nux vomica and strychnine (page 17).

Next to the effect upon the intestine, the most important *rôle* played by morphine in therapeutics is that due to the gentlest degree of its action on the brain. Here, too, the indications are quite general in their nature, and contra-indications scarcely exist. Pains of every kind, tendency to cough, and other unpleasant and troublesome sensations, are often suppressed by 5-10 mg. ($\frac{1}{12}$–$\frac{1}{6}$ grain).

Among the conditions of mental excitement the usual forms of *nervous sleeplessness* can be mastered, at any rate at first. After continued use, both in these and other cases, there comes on a toleration of the remedy, and this keeps on growing. Hence a continuous increase of the dose is necessary in order to achieve the desired effect. In many cases ultimately as much as 1·10 to 1·59 g. (15–22 grains) of morphine may be injected hypodermically in a day.

From the outset larger doses are necessitated by the special *states of mental excitement*, because, as above indicated, the mental functions are sometimes less easily affected by the action of morphine than are the sensory areas. To this category of conditions belong, above all, delirium tremens and atropine poisoning; but other forms of mania also belong to it. On the other hand, its use in tetanus has quite another significance, since tetanus can occasionally be induced by morphine, so the morphine does not help to remove it. In this case it can only be a matter of alleviating the sufferings of the patient by means of the beneficent action of the remedy.

As a supplement to the preparations of the morphine group, we may here find a place for INDIAN HEMP and LACTUCARIUM, since they are at times still employed as narcotics. Along with small quantities of a strychnine-like base, found at any rate in certain varieties (Hay) and along with the volatile alkaloid cannabine, of which we have no definite particulars as to its action (Siebold and Bradbury), *Indian hemp* contains as its peculiar active constituent an amorphous, resinous, bitter-tasting mass (Martius). This substance induces in man first of all a condition of excitement of the mental functions, the symptoms of which are delirium, noisy mirth, at times a depressed mood, flights of the imagination, hallucinations of sight, of hearing, and of movement (flying, swimming, and riding); then follow depression, drowsiness, and sleep. After considerable doses of the resinous substance (0·3 gramme = 5 grains) a high degree of acceleration of the pulse, excessive restlessness, excitement, weakness, convulsions with trismus, absolute loss of power, then sleep, followed by recovery, have been observed (Buchheim and Kelterborn).

Sleep never seems to result in any case until after the state of excitement, provided preparations at all active are made use of. In commerce these are rarely to be got.

Cullen's dictum (1772) regarding *lactucarium* is true at the present day, that the success of this remedy in therapeutics has not yet been proved beyond doubt.

THE ALCOHOL AND CHLOROFORM GROUP.

To this group belong numerous compounds of the fatty series. All gaseous and fluid *hydrocarbons*, the monatomic *alcohols*, their *ethers*, neutral *esters*, *ketones*, and *aldehydes*, and finally, the *halogen derivatives* of all these compounds, act in the same way if they become absorbed at all. Their absorbability depends, however, on the one hand, upon their volatility, and, on the other hand, upon their solubility in water. Of the petroleum hydrocarbons, for example, we can only include here those which evaporate freely at the ordinary temperature. Paraffin and the paraffin oils, on the other hand, are quite inert.

The *local actions* of these substances are due to very varying properties, and these must be carefully distinguished from their actions upon the central nervous system.

Concentrated *alcohol* withdraws water from the tissues : this causes the albuminous elements to coagulate, and so brings about violent irritation and inflammation. *Chloroform* precipitates more particularly the globulin substances, and apparently also myosin, for when it is injected into the arteries of the limb it induces muscular rigidity (Kussmaul). *Ether* coagulates egg albumen.

The more *volatile substances* penetrate rapidly into the tissues, and as a consequence have a more or less irritant action, resembling, so to say, foreign bodies in a molecular form. On this is based the employment of ethereal and spirituous fluids as lotions and embrocations for the purpose of causing a moderate, but not altogether superficial, *irritation of the skin.* The volatile compounds which have a high molecular weight—as, for example, chloroform and chloride of ethylene—cause a transitory but very intense irritation of the skin, and this is succeeded by a lowering of the sensitiveness, hence their use as *local anæsthetics.* When used in the form of a spray the result is *anæsthesia*, due only to *the cold.* Ether is generally used for this purpose. The more volatile substances are, however, better adapted for this, when they have a less solvent power for water than ether has, for condensation of the water vapour of the air results in proportion as the fluid used as a spray is able to take up water, and through this considerable heat is set free and the cooling prevented.

The violently irritant actions of many *allyl ethers*, *e.g.*, oil of mustard, and many *aldehydes* (acrolein), are due to special molecular properties of these compounds.

The *aroma* or bouquet of wine, the *flavour* of vegetables and fruits, and the *pleasant odour* of those essences which are called perfumes, are all dependent for the most part upon unknown ethers and esters of the fatty series. Common ethyl-ether is used for *inhaling* by the *nostrils*, and is said to be very refreshing and stimulating. The mixture of spirit of wine and ether, which is also given internally, and known under the name of *Hoffmann's drops*, enjoys a very great reputation in this respect.

In consequence of the irritation of the mucous membrane, *acute and chronic catarrhs of the stomach* often result from the immoderate use of alcoholic drinks, and this occurs the more easily with brandy drinkers, because of the concentration of the alcohol in the drink they use. Beer drinkers, on the other hand, are as a rule spared from such affections, and enjoy, as compared with the former, good nutrition.

The *behaviour and the fate of these compounds in the body* vary very much, according to the nature of the substances themselves. On the whole, very little is known about the matter.

When *alcohol* is taken, one part is totally consumed to form carbonic acid and water, and the other part is excreted again unaltered with the urine and through the lungs. Its diffusion through the body is essentially a uniform one. As a rule the blood contains greater quantities than the organs, and only at times is the reverse the case (Schulinus).

In consequence of the volatility of *chloroform*, and its solubility in water, it leaves the organism probably for the most part unaltered. Its relation to defibrinated blood is peculiar : in the presence of atmospheric air it causes a solution of the red blood corpuscles (Böttcher). It retards the passage of the oxygen from the oxyhæmoglobulin to easily oxidizable substances, and forms a peculiar compound with the colouring matter of the blood. These changes of the blood cannot be proved to take place in the living body. Moreover, many other substances of this group cause a solution of the blood corpuscles under like circumstances.

Chloral hydrate is not decomposed in the blood into chloroform ; only a small quantity passes unchanged into the urine (L. Hermann); another part undergoes decomposition, with the consequent appearances of chlorides there (Liebreich); while apparently the bulk of this substance appears in the urine as trichlorethyl-glycuronic acid (v. Mering, Külz).

Under the action of *nitrite of amyl*, and other nitrous ethers, the blood assumes in the living body a chocolate brown colour, it loses its power to fix oxygen, and it yields brown hæmoglobin crystals, which show the spectrum of the nitrilic blood (Gamgee). These alterations, which occur without the blood corpuscles being destroyed, are due to the formation of *methæmoglobin* ; this latter disappears again after a time, because it becomes changed back into oxyhæmoglobin (Giacosa). These brown crystals consist probably of methæmoglobin, which has lately been obtained in crystals (Hüfner).

These actions, which are dependent for the most part upon a few inorganic constituents, are able to annihilate to a greater or less degree the characteristics of the group, so that there may be great doubt as to the pharmacological relationship of these substances. Yet the fundamental character can always be easily recognised even in amyl nitrite. It is only when the irritant action entirely predominates, as is the case with the oil of mustard, that we see the pharmacological affinity of such compounds of the fatty series disappearing.

The effects upon the central nervous system consist in the destruction of the functions of the brain, spinal cord, and medulla oblongata, one after the other. Moreover, reflex action is from the very first lessened, and at last annihilated. In this lies the essential distinction between the alcohol and the morphine groups. The order in which the separate functional areas of these organs are attacked is not the same in the case of all the substances. In general, to begin with, the sensitiveness to pain and to other impressions of a similar nature is lessened. Then the control over the voluntary movements becomes less and less, and the psychical functions fall into disorder through the prevalence of uncontrolled conceptions. Then the sensory perceptions disappear, and consciousness vanishes, but dreamy ideas last for a little longer. Last of all, even these and the reflexes disappear entirely.

The *vessels* of the face, of the skin, and probably also of the surface of the brain, begin to dilate at a very early period, in consequence of the lessened irritability of the central origins of their nerves. Hence these parts are seen to be red and turgescent at the commencement of the typical action of alcohol and chloroform. Even a few drops of amyl nitrite inhaled as vapour suffice to bring about this state; at first without any other accompanying effect. Later, according to experiments on animals, the paralysis of the nervous centres for the vessels extends to *all the vessels*, and these entirely lose their tonus, and ultimately undergo extensive dilatation. In consequence of this, the *blood-pressure* continually sinks, and, especially under the effect of chloroform and chloral hydrate, may fall so low as to be only a little above the abscissa of the manometer. At the same time, however, every contraction of the heart causes a strong elevation of the pulse, because the wall of the vessel, when totally relaxed, experiences much greater dilatation through the blood wave than it does when in the tense condition where the pressure is high. Probably the high degree of relaxation and dilatation of the vessels does not depend upon the paralysis of the centres of their nerves, but upon the direct actions of the substances of this group upon the muscular tissue or nerve ends in the walls of the smallest arteries.

In the more advanced degrees of this action, the motor ganglia of the *heart* become paralysed; and this is specially easy to prove in frogs. Yet the weakening or cessation of the action of the heart caused thereby plays a not unimportant part in the case of mammals and mankind, under certain conditions which will be referred to subsequently.

But it is characteristic of the typical action of the substances which belong to the chloroform and chloral group that the *respiratory centre is the last of all the parts of the central nervous system to be deprived of activity.* If *chloroform* be administered steadily till death results, the respiration becomes slower, but remains perfectly regular till the deepest narcosis comes on. When the blood-pressure sinks very low, disturbances of the circulation occur, hence the frequency of the inspiration increases, as is the case in suffocation. At last the respiration takes on an agonized character, and ceases before the heart has left off beating.

The behaviour of the respiration thus described renders it possible, without any appreciable danger to life, to keep up, even for a lengthened period, *the deepest degree of narcosis*, such as is usually caused by chloroform in man when it is administered in practice, especially for the suppression of pain during surgical operations. In this state the sensations, consciousness, and the voluntary and reflex movements, have disappeared. The whole body becomes limp through loss of muscular tonus; the pupils narrower, the respiration less frequent, though regular, and the number of the beats of the heart fewer, though remaining still vigorous.

If the narcosis be gradually brought about by the *inhalation oj dilute chloroform vapour*, and yet the above-described stage be overstepped, the respiratory movements always cease while the heart continues to beat. This stoppage of the respiration can be easily removed by the proper manipulations being carried out at the correct time. But if, on the other hand, there occurs a powerful *inhalation* of *concentrated chloroform vapour*, great quantities of the substance ·get suddenly into the blood of the lungs, and so into the left side of the heart. In consequence of this, the latter suddenly ceases to act before anæsthesia has advanced any further, and therefore before it has caused deep narcosis.

When the *heart* once stops, artificial respiration alone is not sufficient to remove the asphyxia, because through the deficiency of the circulation the chloroform is unable to be got rid of from the heart, that is, the *causa nocens* cannot be set aside. The most efficient remedy is pressure upon the thorax carried out rhythmically for a long time. By means of this the heart is alternately emptied and filled. In giving chloroform care must always be taken that the *vapour* be inhaled only after being sufficiently *diluted with air*, so that the chloroform passes the left side of the heart in small quantities, and finds time to diffuse itself uniformly in the body.

What we have said of chloroform is essentially true of the remaining anæsthetics of this group.

All those *compounds which contain chlorine*—as, for instance, chloride of ethylene, chloride of ethylidene, as well as chloroform—have a much *more paralysing influence* upon the heart, than have those ethers and alcohols which contain no halogen; moreover, the latter do not lessen the vascular tonus so much. In this respect *ethyl ether* deserves the preference which the Americans grant it as compared with chloroform, yet it has this disadvantage,—that because of its low boiling-point, 35° C. (= 95 F.) and its low vapour density, narcosis is far more difficult to cause by it than by substances which have the boiling-point 62 C. (= 144 F.) and the vapour density of chloroform.

When anæsthetics are employed for the purpose of causing a deep narcosis to be kept up for several hours, special *attention* must be paid *to the consequent lowering of the blood-pressure*, because it can be injurious in many cases. According to experiments made upon pregnant rabbits, death of the uterine contents may be caused by a single deep chloroform narcosis without the mother animal herself succumbing (Runge). If narcosis be kept up with care, so that the blood-pressure does not sink too deep, the fœtus remains alive. During pregnancy ether is to be preferred as a rule to chloroform, because of its having less influence upon the circulatory organs, although perfect absence of danger cannot be guaranteed even with it.

CHLOROFORM AND ARTIFICIAL RESPIRATION (DOG).

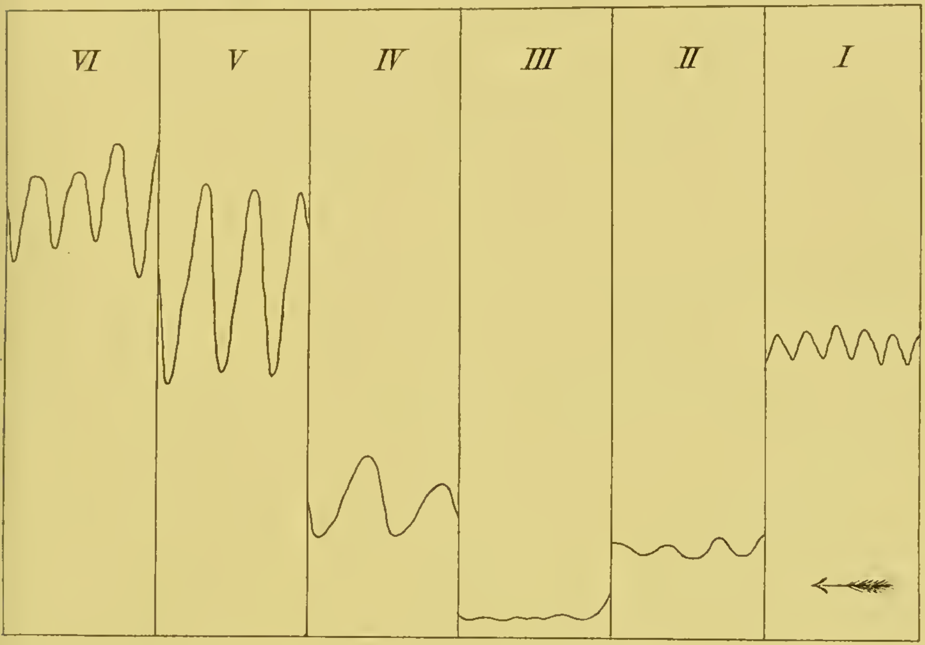


FIG. 1.—Showing the power of artificial respiration in chloroform poisoning.

I. Moderate chloroform narcosis. Blood-pressure 66 mm.
II. Deeper narcosis. Blood-pressure 22.
III. Very deep narcosis; cessation of heart's action. Artificial respiration begun after total standstill of the heart.
IV. V. and VI. show the slow continuous recovery under artificial respiration.

CHLOROFORM (PREGNANT RABBIT).

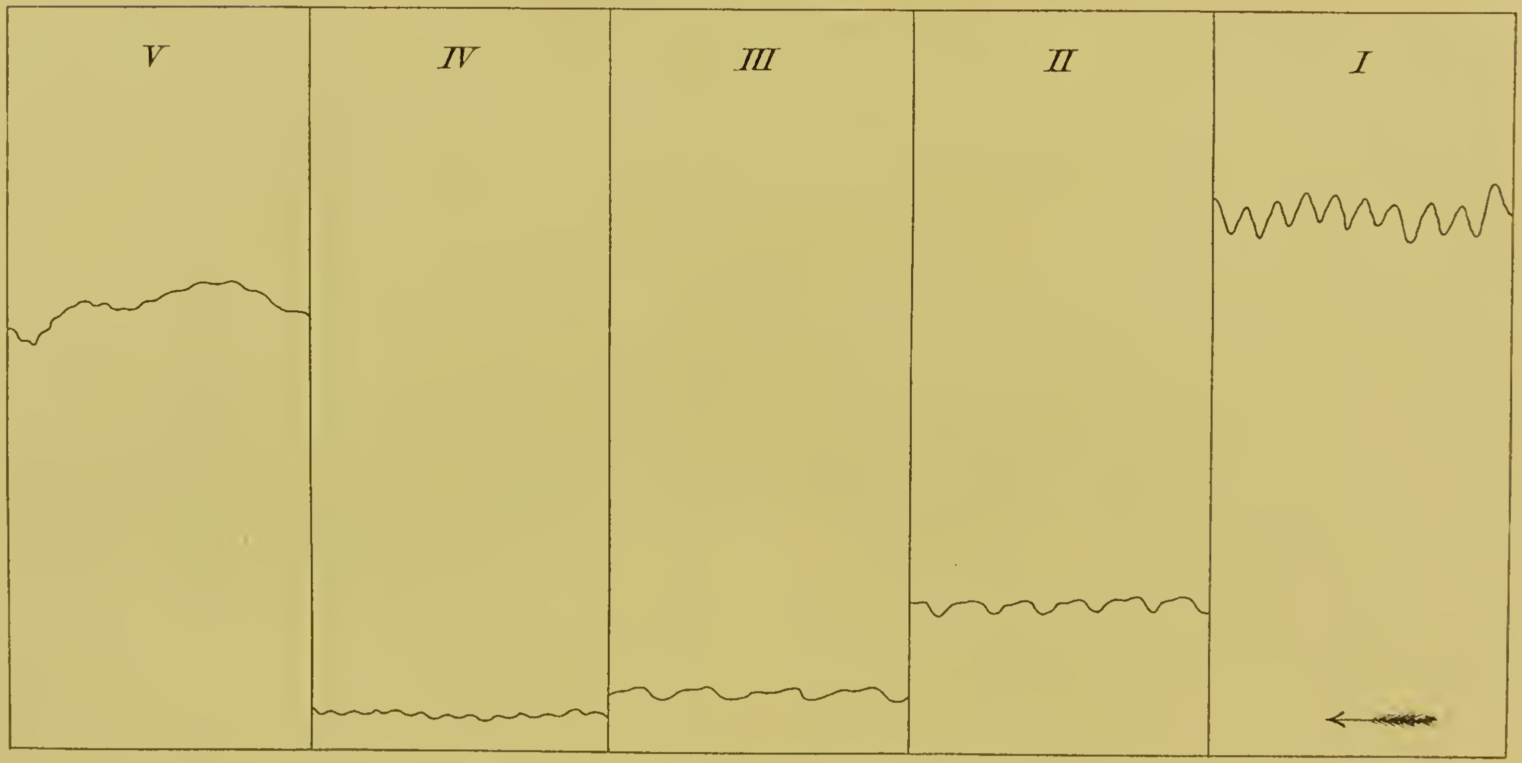


FIG. 2.—Showing that the excessive reduction of blood-pressure under the influence of chloroform may cause death of the fœtus.

I. Before the chloroform. Blood-pressure 110.
II. Five minutes after the commencement of the experiment. Blood-pressure 30.
III. Seven minutes later, young rabbit. Blood-pressure 10.
IV. Three minutes later. Blood-pressure 8. The young in the uterus are dead.
V. Ten minutes after the cessation of the experiment. Blood-pressure 100. The mother rapidly recovering.

The *lighter degrees of narcosis*, in which the irritability of the cerebral centres for consciousness and perception is weakened, but not altogether destroyed, induce *sleep* in a similar way to the corresponding stages produced by morphine. Since the substances of this group lessen at the same time reflex irritability, they are particularly suitable as hypnotics, when the sleeplessness is partly due to a condition of increased reflex sensitiveness (nervousness). In this respect they differ very essentially from morphia, which in large doses increases the reflex irritability, and which in small doses certainly does not lessen it.

In consequence of the paralysing effect upon the reflex apparatus, tetanic spasm becomes more or less effectually suppressed during the deep narcosis caused by chloroform or other substances. The practical employment of chloroform for this purpose suffers a very important limitation from the fact that in tetanus—at any rate in poisoning by strychnine—the nervous centres for the vessels become ultimately paralysed, and that chloroform can increase the danger threatening in this direction because it does the same.

Deep narcosis can be most safely caused, and again quickly got rid of, by the inhalation of chloroform and similar very volatile substances, which are insoluble in water. Substances of this nature are not as a rule suitable as hypnotics, because in their administration they induce great irritation in the stomach; consequently, for this purpose substances are chosen which, being soluble in water, diffuse in the stomach more uniformly, and which, not penetrating so rapidly into the tissues as do the volatile ones, cause less irritation than the latter. To these circumstances chloral hydrate owes its great importance as a hypnotic. But even in small doses it exerts a paralysing action upon the heart and vessels, and so in many cases causes great danger. In consequence substances containing no chlorine have come into use latterly as narcotics. Among these there is first of all *paraldehyde*, which induces sleep well without prejudicing the action of the heart or vessels. *Ethyl carbaminate* (*urethan*) offers the same advantages, and lacks the ill smell of the paraldehyde. All these soporifics of the alcohol group differ from morphia in the fact that they are not nearly so effective in suppressing sensations of pain.

Common *alcohol* is not regularly employed in a medicinal form as a *soporific*, because it lingers a long time in the body. It is therefore not well borne by patients, on the one hand, because of its influence upon the mucous membrane of the stomach, and, on the other hand, because of its known disagreeable after effects, which so often cause a disgust against the use of alcoholic drinks.

Stimulant and refreshing effects are ascribed to alcohol, and it is much employed, therefore, in the form of wine in exhausting diseases, for the purpose of strengthening the action of the heart, of stimulating the nervous system, and of increasing the strength in general,—especially, therefore, in convalescence. In this we proceed upon certain experimental data, without defining more closely the manner and means in which the result takes place. For example, it remains undecided whether the use of wine during convalescence makes the recovery in certain cases a possibility, or whether it merely accelerates it, or whether it be merely a question of an improvement of the patient's general feeling.

Moreover, the pleasant, though not always beneficial, results after using *alcoholic drinks as beverages* are usually ascribed to its stimulating action. In regard to this, appeal is made to the appearances which are observed under such conditions, especially to certain excited states of the mental functions, such as noisy and incessant talkativeness and demonstrativeness, to the increased frequency of the pulse, the turgescence and redness of the surface of the body and of the face, as well as to the increased feeling of warmth. Closer observation of these appearances teaches, however, that they are merely the results of the commencing paralysis of certain portions of the brain.

In the *mental areas* the finer degrees of *observation*, *judgment*, and *reflection* are the first to disappear, while the remaining mental functions remain in a normal condition. This is sufficient to explain the often strange conduct of persons who are under the influence of alcoholic drinks: the soldier acts more boldly because he notices dangers less and reflects over them less; the orator does not allow himself to be influenced by any disturbing side considerations as to his audience, hence he speaks more freely and spiritedly; *self-consciousness* is lost to a very great extent, and many are astounded at the ease with which they can express their thoughts, and at the acuteness of their judgment in matters which, when they are perfectly sober, with difficulty reach their minds; and then afterwards they are ashamed at their mistakes. The drunken man imagines he has great muscular powers, and exhausts himself by unusual and useless exhibitions of his strength, without considering that they may do him harm: a sober man, on the other hand, is always anxious to spare his strength.

The *insufficient control of the feelings* lends a peculiar character to the mental aspect of the drunken man. Consequently we see at one time cheerfulness, at another time sadness, without any reason; at one time he is most pugnacious, at another he shows unusual friendliness. Yet the man of good breeding knows how to control himself in these cases better than an uncultured man.

However difficult it may be to prove a directly stimulant effect on the mental areas through alcohol, still more is this the case with regard to the other functions.

The *rise in the frequency of the pulse* is not dependent upon the action of alcohol, but is caused by the circumstances under which the alcoholic drinks are usually consumed. It is the result of the energetic behaviour, and, according to the investigation made hitherto, it is not present when the body is quite at rest (Zimmerberg). The *turgescence and redness* of the face, as stated above, are caused by loss of the tonus of that part of the vascular nervous centre from which the vessels of the skin and of the face receive their nervous supply. The increased flow of blood to the surface of the body, along with the lessening of the heat-sense, causes a feeling of pleasant warmth, where before, through the lowness of the external temperature, there was a disagreeable feeling of coldness. Therefore this effect of alcohol, which is specially valued by the inhabitants of cold countries, and which the laity are most readily inclined to consider as a result of stimulation, is only dependent upon a sort of paralytic condition of the areas concerned.

Hence, if no directly stimulant effect of alcohol upon any organ can be proved, we cannot consider the beneficial results of its action at the bedside as dependent upon it. It is true enough that in wine, one of the most important substances in this category, unknown forms of ethers are present, which probably act somewhat differently from the alcohol itself. Nevertheless it is perfectly safe to assume that in this direction they will in no way differ from the analogous compounds. The kinds of wine to which a strong stimulant action is ascribed, and which, as is said, are felt going to the head, cause from the outset, just as does amyl nitrite, a great dilatation of the vessels of the face, and presumably, too, of the membranes of the brain. Those symptoms which have been explained as being due to stimulation are closely connected with this effect.

It is quite a different thing to answer the question as to how the beneficial and curative effects due to using wine in sickness, especially in weakness of the heart, are to be explained upon the ground of a paralysing action on the part of its constituents. The answer to this question is hard to find, because we have only empirical rules to guide us, and these afford no idea as to the nature of the condition which is removed under the influence of wine.

If the depressed *action of the heart* is to be aroused, we do not know as a rule what are the morbid changes at the bottom of the weakness of the heart which form the point of attack for the wine or alcohol. Possibly the paralysing influence of the constituents of the wine upon the nerves of the blood-vessels removes a *vascular spasm*, which is presenting great obstruction to the emptying of the heart, or possibly it may alter favourably the *general distribution of the blood in the organs*. In other cases it may be a matter, perhaps, of the *lessening of a too strong tonus of the inhibitory nerves of the heart*, or of a *lessening of a state of irritation of the motor ganglia of the heart*, which state, like electric irritation, makes the pulsations frequent and superficial. Yet the following supposition remains possible, viz., that alcohol and the volatile ethers stimulate the *muscle of the heart* directly ; for no investigations have as yet been made as to the behaviour of the latter under the influence of small doses of those agents. The voluntary muscles of the frog are not paralysed, but rather gain in working power.

No one will expect any special advantage, we imagine, *from a stimulation of the sensations and of the mental functions in disease*. We aim rather as much as possible at protecting from every form of excitement those areas which are usually in a state of increased sensitiveness, and consequently keep all strong stimuli arising in the outer world as carefully as possible away from the patient. These efforts are assisted by a mild narcosis, which the taking of the wine brings about, even though it be no more than a slight deadening of the hypersensitiveness. Just as rest enlivens and refreshes, so can wine have a like effect by favouring the conditions for rest, although it does not stimulate any function directly.

Finally, the *importance of wine merely as an article of luxury* cannot be highly enough valued. It seems even doubtful whether, if taken in any other way—for example, subcutaneously—it would have in all cases the same or in fact any enlivening effect at all. Through the sensations arising from the enjoyment of the odour and flavour of the wine, and through a very delicate degree of the above-mentioned narcosis, it is probable that innumerable reflex processes of every possible kind are begun or are arrested, and that thereby, in consequence only of the average general result of these effects, a powerful influence must be exerted upon the course of a disease.

The *indications for the administration of wine* as a stimulating, enlivening, and strengthening remedy are of quite a general nature. When, either in an acute or a chronic disease, we wish a strong action upon the nervous system, we choose the strong southern wines, which contain eighteen to twenty-two per cent. of alcohol; in these cases we also often give subcutaneous injections of ether. If the wine is to be taken more as a beverage, then the full-bodied German and French red and white wines should be preferred, the latter especially in feverish affections, the former when chronic catarrhal conditions or states of the digestive organs seem to make a slight astringent effect desirable.

While in earlier times the use of alcoholic drinks, and even of wine, was considered harmful in *acute feverish inflammatory affections*, in later days alcohol has been much recommended, in the form of brandy and cognac, by English and French physicians, in the treatment of inflammation of the lungs and articular rheumatism. This treatment is based upon the fact, proved experimentally upon men and animals, that alcohol in large doses lowers the temperature and lessens metabolism. Nevertheless this effect can only be made to show itself when such quantities are employed as evoke a very perceptible degree of intoxication.

A glass of strong brandy administered immediately after *severe injury* may occasionally afford great assistance in blunting sensation and in lessening reflex irritability, and may also exert a beneficial influence upon the subjective feeling of the patient.

Among the substances which have the typical action of the group very essentially modified through a special component, the most important at present are *nitrite of amyl* and *iodoform*. In the case of the former, undoubtedly one portion of the action, especially the convulsions which occur along with the narcosis, and probably also the diabetes, are dependent upon the already mentioned alterations in the blood. The energetic action of this ether upon the vessels is very characteristic of it. If a few drops be inhaled, it causes in man a great feeling of heat, and frequently a flaring redness of the face ; at the same time the vessels of the surface of the brain become dilated (Schüller, Jolly, and A. Schramm). There is no ground for assuming a stimulation of the vaso-dilator nerves as the cause of these appearances. Moreover, the blood-pressure very soon sinks, and in connection with this a direct action upon the walls of the vessels is at work (L. Brunton).

This energetic action upon the vessels remains limited to the above-mentioned area, and is accompanied by a great rise in the frequency of the pulse ; and attempts have been made to take advantage of it, after the precedent of Richardson, Gamgee, and Brunton, in a considerable number of cases which, it was believed, were connected with spasm of the vessels. Among these must be mentioned more especially angina pectoris, asthma, hemicrania, and epilepsy. Up till now, in spite of favourable accounts as to the results, no certain indications have been obtained for the use of this remedy.

Iodoform, which at present plays so important a *rôle as an antiseptic in the surgical treatment of wounds*, does not cause a typical narcosis, but a severe form of mental disturbance, the symptoms of which consist in restlessness, delirium, hallucination, melancholy, and insanity. It also paralyses the heart very powerfully and especially its motor ganglia, just as does the monoiodaldehyde, called iodal, the effect of which on the heart of the frog has been very thoroughly investigated.

All the other halogen derivatives participate with *iodoform* in having antiseptic properties. Yet, probably, the action is increased to an important degree through iodine being given off, and appearing in the form of compounds with the alkalies or with albumen. This circumstance, as well as the slight solubility and slight volatility of iodoform, determine its *importance* as a *local antiseptic*, for it can be applied in the form of a dusting powder in quantities sufficient for disinfection, lasting a considerable period. At the same time it is absorbed from the wounds, slowly it is true, but in sufficient quantities, when applied directly over extensive areas, to bring about the already mentioned grave symptoms of *poisoning*. These are probably dependent upon iodoform itself, while the coincident exanthemata are to be referred to the iodine, which is given off in the form of alkali or albumen compounds. Along with iodides there appears in the urine a "conjugate glycuronic" acid which contains iodine. It is probable that for the treatment of wounds iodoform can be replaced by less poisonous chlorinated compounds of similar composition.

Before leaving this subject it may be well to notice that occasionally, though very rarely nowadays, oxychloride of carbon ($COCl_2$) is present in chloroform. It is a gas readily known by its suffocating smell, and is formed under the influence of light. This substance occurs regularly, along with hydrochloric acid, when large quantities of chloroform evaporate in a confined space in which a large flame is burning, *e.g.*, during operations by gaslight. The more important impurities of chloroform are the chlorinated products of the methane and ethane series. These, however, act like chloroform. But tetrachloride of carbon (CCl_4) should not be lost sight of, because it paralyses the heart more powerfully than chloroform (Simpson, &c.). Its detection is based upon the boiling-point (77 C. = 171 F.), its specific gravity (1·629), and its not being altered by the action of caustic potash.

THE CAFFEINE GROUP.

To this belong *caffeine* and *theobromine*. Chemically these substances are closely related, for the latter is *dimethylxanthine* and the former *trimethylxanthine*, and, as regards their actions, they differ from each other only quantitatively.

The plants which contain these two neutral substances, so closely related to the nitrogenous metabolic products of animal life, yield very highly valued articles of luxury in every region of the globe. The products of the *tea shrub* and of the *cacao and coffee trees*, as is well known, control the markets of the world. The *gurru or cola* nuts, which come from the *Cola acuminata*, get disseminated by the inhabitants of Central Africa along commercial routes all over the interior of that part of the world as a valuable article of luxury (Schweinfurth). America yields *cacao*, which contains theobromine, and along with this *guarana paste*, prepared from *Paulinia sorbilis*, containing both caffeine and theobromine, and again the dried leaves of *Ilex paraguayensis*, known under the name of *yerbamaté* or *Paraguay tea*. All these are of great local importance. Caffeine also occurs in the North American *Apalachian tea* and in the South African *Bush tea*, the former of which comes from various species of Ilex, and the latter from Cyclopia.

Caffeine causes, on the one hand, like strychnine, a great increase of the reflex irritability of the central nervous system, and as a consequence *tetanus*, and, on the other hand, a peculiar *muscular change*, which in frogs very closely resembles the *rigidity* due to heat or to death.

In the *Rana esculenta* at first merely a typical tetanus comes on without any other symptoms. In *Rana temporaria*, on the other hand, there supervenes only the change in the muscles without a trace of increase of irritability. In the milder degrees of poisoning these differences between the two kinds of frogs gradually disappear.

The muscular rigidity begins at the point of application, and spreads slowly from it to the neighbouring, and then afterwards to the more remote organs. Not only individual muscles, but even portions of one and the same muscle, often remain quite intact, while the neighbouring ones are already seen to be rigid, and have lost their irritability either entirely or only in areas.

In the *heart of the frog*, as a rule, merely slowing of the beat is to be noticed. Only after very great doses is a rigidity to be seen similar to that in the other muscles. Upon isolated bundles of muscle fibres a solution of one part of caffeine in 4000 of blood serum acts as violently as boiling water.

In *mammals* the *tetanus* predominates; yet death is caused through *paralysis of the heart* after the injection into the blood of 0·08–0·1 g. per kg. ($\frac{1}{2}$–$\frac{3}{4}$ grain per lb.) of body weight in the case of cats and rabbits, and in that of dogs after half of this amount.

Small doses cause a *striking rise in the frequency of the pulse*, and this occurs even in animals which have been atropinised; from which it is evident that it does not act by preventing inhibition. The blood-pressure sinks from the very first: after this a rise occasionally takes place (Leven, Johannsen). In all cases, however, action of the heart is irregular and arhythmical (Johannsen, Aubert), just as in the last stages of the action of digitaline. The injection of caffeine into the blood causes in rabbits a reduction in the amount of contraction of the muscles (Rossbach). In frogs very small doses increase their working power (Kobert).

In *man*, after internal doses of 0·5–0·6 g. (8 or 9 grains), states of *excitement resembling intoxication* have been observed, consisting in giddiness, headache, buzzing in the ears, trembling, restlessness, sleeplessness, confusion of thought, delirium, and at last drowsiness (C. G. Lehmann, L. Lehmann, &c.) In some cases these doses have almost no effect (C. G. Lehmann, Aubert), and even a quantity of 1·5 g. (23 grains) did not cause any great degree of poisoning (Frerichs).

The appearances on the part of the *vascular system* consist, as in animals, in throbbing of the heart, increase in the frequency of the pulse, and in irregularity of the cardiac action.

The frequently observed *desire to micturate* is worth noticing. It occurred in a very pronounced degree in a case of poisoning, and came on with an increase in the quantity of the urine. Chinese tea has been recommended as a *diuretic* in the same sense as digitalis (Percival). Caffeine has lately been brought into use for this purpose, and in some cases a good result has been achieved. It acts directly upon the kidneys (v. Schroeder).

The *importance of caffeine and theobromine* in the articles of luxury, coffee, tea, and chocolate, is to be referred to the changes in the muscular and nervous system already described. When, in consequence of weariness of the body and of exhaustion, the stimulus of the will is being conducted by the nervous system only tardily to the muscles, and when the latter are in such a state that they can only with difficulty put what is left of their potential energy into action, then caffeine, on the one hand, removes this increased resistance in the central nervous system, the irritability of which now increases, and, on the other hand, it makes the muscles disposed to pass from the relaxed into the contracted state more easily. The latter result will be lasting if the effect be too strong. While acting thus, the remedy does not necessarily increase either the irritability or the absolute working power of the normal muscle.

A cup of filtered infusion of coffee from 16·5 g. (half an ounce) of roasted beans contains 0·1–0·12 g. (1½–1¾ grains) caffeine, and there is just as much in a cup of an infusion prepared from 5 to 6 g (⅙ of an ounce) of tea leaves (Aubert). These quantities seem sufficient to cause that degree of effect which alone can be beneficial, for after 0·5 to 0·6 g. (8 or 9 grains) of caffeine, symptoms of severe poisoning sometimes occur.

Then, in connection with coffee and tea, certain *volatile constituents* also come into consideration. In the former there are aromatic smelling and *empyreumatic products* which result from the roasting. In tea, on the other hand, and especially in the green sorts, there are the *ethereal oils*, previously formed in the leaves or due to blossoms which have been added. They act by stimulating the brain, and consequently are of importance in the exhausted states of this organ. This stimulation forms a contrast to the action of alcohol, which to a certain extent is removed by an infusion of coffee (Binz). Just as alcohol and the substances which belong to that group induce sleep, so strong coffee or an infusion of green tea drives it away.

The importance of coffee as a *remedy*, apart from its importance as a diuretic, is to be found alone in the same property as leads to its use as an article of luxury. The favourable results which have been seen in a few cases of *migraine*, in which the attack has been cut short by the employment of caffeine and guarana, can be the less explained, seeing that the nature of the affection itself is still totally obscure.

THE CAMPHOR GROUP.

The substances which belong to this group are *stimulants of the central nervous system*, especially of the various functional centres in the medulla oblongata.

In mammals and man epileptiform convulsions occurring at short intervals so influence the aspect of the poisoning, that the disturbances of the respiration and of the frequency of the pulse, which are dependent upon the stimulation of the respective areas of the medulla, are not directly recognisable at all. In curarized animals there is to be seen a *periodic rise in the arterial blood*-pressure, dependent upon the stimulation of the vascular nervous centres.

Excited states of the mental areas precede the convulsions both in animals and in man. A great impulse to keep moving about is a characteristic phenomenon. Dogs trot incessantly round the walls of the room ; giddiness, headache, confusion of ideas, delirium, at first a rise and then a fall in the frequency of the pulse, redness of the face, loss of consciousness, and convulsions are the usual appearances in man after small doses.

In *frogs* there comes on very soon a *curarine-like action* on the part of the camphor, preceding the outbreak of the convulsions; and no matter how the drug be applied, the *cardiac muscle* experiences a *stimulation* which causes the heart to commence beating again after it has been made to stop by muscarine, or in consequence of paralysis of the motor ganglia, or through the lowering of the muscular irritability.

To judge from these effects the *therapeutic importance* of camphor must be sought in the fact that the strengthening of the respiration, and of the activity of the heart, in conditions of collapse such as occur in the course of acute exhausting diseases, is brought about through simultaneous stimulation of the centres of respiration and of the nerve centres for the vessels, as well as for the cardiac muscle. Moreover, it is to be sought in the fact that a paralysis of the nerve centres in the vessels, so seldom absent in such cases, is counteracted by it. The beneficial effects of this remedy, then, depend upon an increase of the blood-pressure, and upon the acceleration of the circulation, and its employment is only limited by the fact that its absorption is subject to great irregularities, because of its very slight volatility at ordinary temperatures, and because of its insolubility in water. Accordingly, the strength and duration of its action cannot be sufficiently regulated. To this must be added the fact that camphor apparently becomes rapidly changed in the body into various camphoglycuronic acids, and through these changes becomes inert. Hence the first symptoms of the action of camphor, such as an increased feeling of warmth and acceleration of the pulse, come on in man sometimes after 0·03 to 0·06 g. (½–1 grain), and sometimes only after 0·35 to 0·70 g. (5–10 grains) (Jörg). Disturbances of the functions of the brain result from doses of 3 to 4 g. (45–60 grains).

To the camphor group belong furthermore *borneol*, *campherol*, *menthol*, and presumably numerous other so-called *camphors*, and probably also various ethereal oils.

Whether *musk* is to be included here has not yet been settled; it seems, however, very probable. It causes in human beings, in doses of 0·05 to 0·90 g. (¾–12 grains), appearances on the part of the pulse and of the brain resembling those of camphor (Jörg).

The apparently quite inactive *castoreum* probably owes its reputation as a stimulant to the fact of its source being analagous to that of musk.

THE AMMONIA GROUP.

We must carefully distinguish between the action of ammonia on the nervous system and the local irritations and caustic actions caused by this volatile base, and also the saline action of its organic salts. In the organism, ammonia becomes very quickly changed into urea under the action of carbonic acid; in the case of dogs no evident action upon the nervous system occurs after doses of carbonate of ammonia, even though they be as great as the stomach can stand, 10–20 g. (150–300 grains) daily; hence it seems doubtful whether such an action comes into play at all in the case of human beings after the usual medicinal doses.

In mammals injection of a solution of ammonia, or of carbonate of ammonia, into the blood or under the skin causes convulsions, in consequence of the irritation of the medulla oblongata and spinal cord, which is seen in the acceleration and spasm of the respiration. They may be associated with tetanus, acceleration or retardation of the frequency of the pulse, and increase of the blood-pressure (Blake, Böhm and Lange, Funke and Deahna). In the case of rabbits 0·05 to 0·07 g. ($\frac{3}{4}$–1 grain) of ammonia in 3 to 4 ccm. (50 to 60 minims) water causes only a slight effect when rapidly injected subcutaneously. But tetanus and death have followed the injection of 0·01–0·015 g. ($\frac{1}{6}$ to $\frac{1}{4}$ grain) into the blood (Funke and Deahna).

Apart from their use as local irritants, the preparations of ammonia, including sal ammoniac, are used at present merely as expectorants. Probably ammonia causes an increased secretion of fluid mucus through its being poured into the bronchi in small quantities, either in the free state or as a carbonate, so that the removal of the mucus by coughing and hawking is rendered easier.

THE PRUSSIC ACID GROUP.

Prussic acid (hydrocyanic acid) is a universal poison to all organisms of the animal and vegetable kingdoms. Consequently it acts also as a preventive of fermentation and decomposition (Fiechter and Miescher). In mammals it causes *first of all a violent irritation of various functional areas* in the medulla oblongata, especially of the respiratory and of the so-called spasm centres, as well as of the central origins of the inhibitory fibres of the vagus, and of the vaso-motor nerves. Violent convulsions with impeded spasmodic respiration are the immediate results of this irritation, which rapidly passes into paralysis of the parts mentioned. To such an action also, though less readily, the motor ganglia of the heart succumb, though the muscular tissue of the latter remains irritable till death occurs. The fatal result is sometimes brought about instantaneously through the cessation of the respiration, and the weakening of the heart's action.

Simultaneously prussic acid forms with *hæmoglobin* a peculiar crystalline *compound* which can indeed take up oxygen, but probably delays the giving off of it again to oxidisable substances in the organism (Gähtgens and Hoppe-Seyler). Even though the change in the blood plays no part in the severer degrees of poisoning, yet it may be of importance when small doses are used for a long time, through its exercising some influence upon the metabolism.

HYDROCYANIC ACID.
(*Rabbit*)

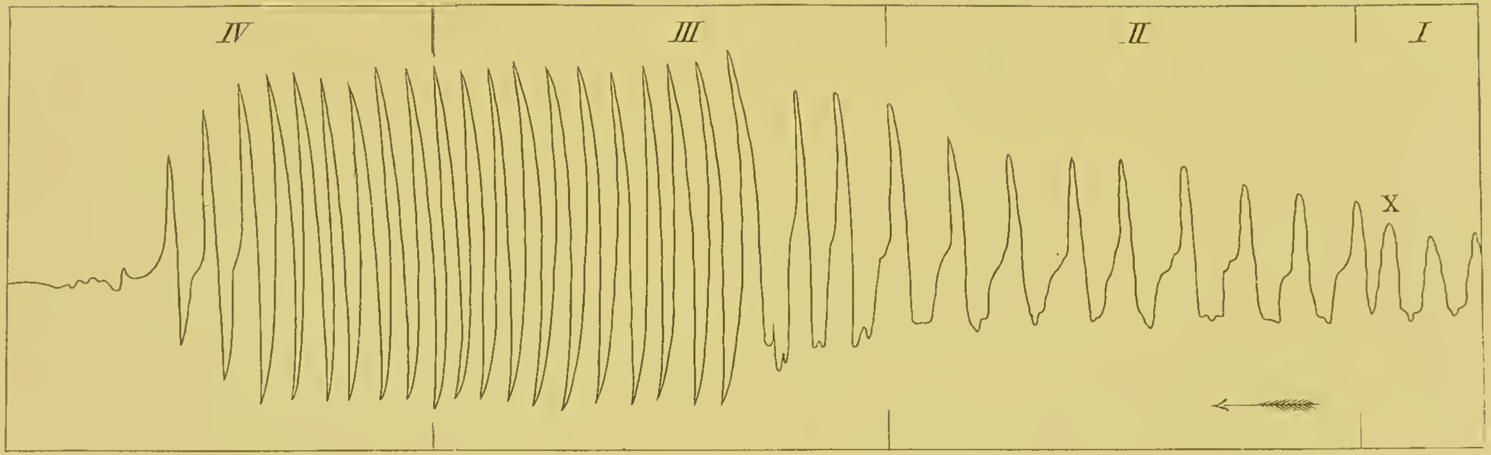


FIG. 3.—The tracing shows the effect of hydrocyanic acid upon the respiration, and was made by a Marey's tampon.

I. Before the inhalation of the hydrocyanic acid.
II. Beginning of the inhalation at X.
III. Violent spasmodic breathing (from the stimulation of the respiratory centre).
IV. Stoppage of the respiration.

Quantities of prussic acid which do not produce any material degree of poisoning have no apparent effect, or cause slight discomfort in the head, giddiness, and a peculiar feeling of oppression in the chest, accompanied by a raw feeling in the throat. Whether the action which causes these symptoms is of any importance in therapeutics has as yet not been decided. Even the usual empirical indications for the employment of this remedy are as yet wanting.

Bitter almonds, though they yield prussic acid, are used only as a flavouring agent.

THE ERGOT GROUP.

The active principles of ergot have only lately been thoroughly investigated. It contains four organic constituents worthy of attention, two being bases and two acids.

Ergotinic acid, discovered by Zweifel, is the leading constituent in Bonjean's "ergotine," and in almost all the so-called extracts of ergot of the European pharmacopœias; it is also the chief substance in the sclerotinic acid of Podwyssotzki, and of the "dialysed ergotine" of Wernich.

When its neutral salts are injected under the skin of *cold-blooded* vertebrates they cause *paralysis of the spinal cord*, followed by *cerebral depression*. The same symptoms are noticed when larger quantities of ergotinate of soda are injected into the blood-vessels or under the skin of *warm-blooded* vertebrates. When this substance is given internally no action follows, because it is probably decomposed by the digestive ferments into sugar and an inert organic base, being a glucoside; this substance breaks up also under the action of acids.

The above-mentioned commercial preparations of ergotinic acid, especially the so-called ergotine of the pharmacopœias, are very reprehensibly employed for subcutaneous injection, seeing that they here induce a powerful local irritation, which is simply dependent upon an acid reaction, and upon other irritant properties due to foreign bodies. Hence the origin of the use for cicatricial contraction in the uterine fibromata, and in telangiomata, &c. of various organs.

Sphacelinic acid (Kobert) is the substance which causes the gangrene due to ergot of rye (*ergotismus gangrenosus*). This affection results from contraction of the smaller vessels, the walls of which become at the same time diseased, secreting on their inner surface a hyaline mass (v. Recklinghausen), which prevents the circulation of the blood through them. In the case of a pregnant animal doses insufficient to endanger the life of the mother cause tonic contraction of the uterus, and the young are consequently expelled.

Ergotinine (Tanret) is an absolutely inert base, pharmacologically speaking; any actions which have been ascribed to it are really due to the presence of the substance to be mentioned next.

Cornutine (Kobert) is an alkaloid, contained, along with ergotinine, in rye. To it probably are due the convulsive forms of ergotism (*ergotismus spasmodicus*). In small doses it causes *salivation*, and slowing of the pulse by *stimulation of the central origins of the vagus.* If the animal is pregnant, *clonic contractions of the uterus* result, culminating, perhaps, in expulsion of the uterine contents. In large doses the alkaloid causes, like veratrine, *muscular rigidity* and *spasms.* Both cornutine and the sphacelinates, *e.g.*, of soda, raise the blood-pressure.

Cornutine and sphacelinic acid can be extracted only by alcohol, and are therefore not contained in the fluid extracts made with water, but are contained in those made by glycerine, alcohol, and water. Since, however, both these principles lose their power after a few months, even these fluid extracts become rapidly inert.

In corn smut, *Uredo maidis*, there are none of the above principles, and in fact no substance at all which exerts any influence on the uterus.

THE ATROPINE OR TROPEÏNE GROUP.

The alkaloid *atropine* which is contained in the *Atropa belladonna* consists in an ester-like combination of tropic acid with a base tropine, and the latter is identical with hyoscine, which is the analogous decomposition product of hyoscyamine. Tropine is almost inert, but if one atom of hydrogen be replaced in it by an acid radical, the resulting compounds show the actions peculiar to atropine (Buchheim). Such compounds of tropine, with various acids, have been made in considerable numbers by a ready process, and have been called tropeïnes (Ladenburg).

Atropine is therefore the tropeïne of tropic acid. It occurs in the belladonna plant, and as daturine in the thorn-apple. *Hyoscyamine* contains the same constituents, but is only isomeric with atropine (Ladenburg). It occurs in a crystallizable and also in an amorphous modification in henbane, and is said to be contained in the thorn-apple, and also to be identical with *duboisine* (Ladenburg).

A further constituent of the nightshade is *belladonnine* or the tropeïne of belladonnic acid (Buchheim).

Of the tropeïnes made artificially from tropine with various acids, and not occurring in the vegetable kingdom, we must more particularly mention *benzoyl-tropine* (Buchheim), and oxytoluyl tropine or *homatropine* (Ladenburg).

The character of this action is the same in all tropeïnes. The deviations are essentially only quantitative in nature.

The *typical action of atropine* affects the very various areas of the central nerve system, and a series of peripheral organs. In the case of the latter, it causes from the outset paralysis of certain nervous elements, and in the case of the former, in the first place stimulation, and subsequently paralysis.

To the peripheral organic areas upon which atropine exerts a paralysing influence belong the mechanism for the adaptation and accommodation of the eye, the inhibitory mechanism of the heart, the special glands, and the motor nerve elements in the organs which contain involuntary muscular fibres, more particularly in the intestine. Muscarine stimulates exactly the same parts as atropine paralyses.

In the eye, *dilatation of the pupil* is caused when the most dilute solutions of atropine are dropped into it, and the ability to *accommodate* for near objects is quite lost.

The dilatation of the pupils is greatest in man, in dogs, and in cats, and is weaker and more transient in rabbits. In frogs it occurs only after large doses; in birds it is totally wanting (Kieser [1804], Wharton Jones, &c.)

This *action is a local one*, and affects the elements of the iris, for the dilatation remains limited to the poisoned eye, and if atropine be put carefully into one side of the eye, it causes dilatation of that side (Fleming). It may often be induced even in the extirpated eye of the frog (de Ruiter). The cause of dilatation is to be found in the paralysis of the ultimate terminations or end organs of the oculo-motor nerve in the iris.

The following facts support this view. When the above-mentioned nerve is irritated inside of the cranial cavity (Bernstein and Dogiel), or when the ciliary nerves are irritated (Hensen and Völckers), the narrowing of the pupil does not take place in the atropinised eye; while when the iris is directly stimulated by four electrodes, of which one member of a pair stands diametrically opposite to the other member, contraction takes place (Bernstein and Dogiel), at least in some cases, when they are placed on that part of the cornea which corresponds to the inner margin of the iris. Hence the sphincter is irritable even after the influence of the oculo-motor nerve has ceased. Yet the sphincter, after strong atropinising, seems to be paralysed just as other involuntary muscles. The frequent absence of the contraction after such direct stimulation of the iris is probably to be referred to this cause.

It is impossible to produce any narrowing of the pupil by means of the oculo-motor nerve, when the eye is under the influence of a dose of atropine, and therefore contraction cannot be caused either by the stimulus of light or by muscarine. On the other hand, physostigmine causes contraction even in the atropinised eye, because it does not act like muscarine upon the end organs of the oculo-motor nerve, but as a direct irritant to the muscles themselves. Hence it causes contraction of the pupil through the preponderating action of the sphincter, which is the stronger. Atropine has no power over the contraction of the pupil in certain animals, *e.g.*, the rabbit, which can be induced by stimulating the trigeminus (Grünhagen).

The *sympathetic* plays no part in the action of atropine upon the eye. Dilatation of the pupil caused or even favoured by irritation of this nerve is from the very outset improbable, because the alkaloid does not give any indication whatever of a stimulant action upon nervous elements in other peripheral organs. It is quite true that section of the sympathetic causes in normal as well as in atropinised eyes a certain degree of contraction of the pupil. Yet from this we are only permitted to conclude that in this nerve the normal tonus, which passes from the central nervous system to the dilator of the pupil, is not destroyed by the poison.

Moreover, the *paralysis of the accommodation* may be considered as dependent most probably upon the paralysing action of the atropine on the terminal apparatus of the oculo-motor nerve. The only way to produce a certain degree of accommodation for near objects while the effect of the atropine lasts, is by means of the action of physostigmine upon the muscles of the eye.

Of all the above-mentioned tropeïne alkaloids, *atropine* is relatively slow in inducing the above-described alterations in the eye, but they last a long time, even for days. In the case of *homatropine* they come on quickly, but also disappear quickly. In this respect *hyoscyamine* appears to take an intermediate position. This character must be considered as dependent on a difference in the facility of the absorption and excretion of the individual substances.

In the *treatment* of *ocular affections atropine is employed* for the purpose of dilating the pupil, and rendering the deeper lying parts more accessible to ophthalmoscopic examination, and also for the purpose of bringing the iris out of reach of the lens. It is also assumed that, in consequence of the blood being pressed out of the vessels of the iris, inflammatory conditions of this organ are improved, and lastly, morbid hardness and tension of the ball of the eye is believed to be lessened under its influence. But it has been shown by means of manometric measurements that the intraocular pressure does not fall (Adamük) but rises (Graser). It cannot, however, be determined in what way the nutrition of the interior of the eye gets altered under these circumstances.

In the frog's *heart*, small doses of atropine paralyse only that apparatus which brings about diastolic stoppage, or at least slowing of the pulse with increase of the diastolic condition of the heart, when the peripheral part of the cut vagus, or the venous sinus of the heart in frogs, is stimulated. Then there are no means, by stimulation or by muscarine, by which the slightest trace of the so-called inhibitory action may be induced. Meanwhile the heart acts in other respects exactly as a normal one.

When these mechanisms are continuously under the influence of stimulation, proceeding from the central nervous system along the course of the vagus, as is, under usual circumstances, the case to a high degree in man and dogs, and in a less degree in cats, the frequency of the pulse after poisoning from atropine increases, in consequence of the absence of this continual tonus of the vagus, and the blood-pressure rises. In men, as well as in dogs, the frequency of the pulse may mount to twice the normal : in rabbits this symptom shows itself only to a slight degree, and in frogs not at all.

Of the tropeïnes, belladonnine acts most feebly upon the inhibitory apparatus, the others almost exactly resemble each other. The paralysis occurs most readily in frogs, with greatest difficulty in rabbits, and tolerably easily in man.

The *secretion of all glands proper* becomes suppressed under atropine. In the case of the *submaxillary glands*, stimulation of the nerves of the glands does not induce any secretion of saliva in atropinised animals (Keuchel), though the blood-vessels of the glands become dilated just as before (Heidenhain). The secretion of perspiration and of mucus ceases, the secretion of the pancreas even, after being increased by muscarine, is suppressed (Prevost), that of the bile is lessened (Prevost), stimulation of the sciatic nerve no longer evokes the secretion of perspiration in the paws of kittens (Luchsinger). The secretion of milk has even been seen to cease after medicinal doses of belladonna (Goulden, 1856). In each of these cases the hyper-secretion caused by muscarine or pilocarpine is promptly suppressed by atropine, and the two former alkaloids remain inert as regards all these glands, if the latter alkaloid has been used beforehand.

The above-described actions cause *very striking symptoms in man:* the pupil is dilated and insensitive to light, the eye dark and brilliant, the pulse frequent and full and hard. The diminution and suppression of the secretions cause difficulty in swallowing, even make it impossible, and cause also dryness of the mouth, throat, and skin. In one case of poisoning, the burning hot skin was here and there covered with perspiration (Gerson). The perspiration which comes on subsequently has the same origin as that in the death agony.

In the organs which have involuntary muscle fibres the *influence of atropine upon the peristalsis of the intestine* is particularly noticeable. The latter ceases totally, when it receives its impulse entirely from the motor ganglia in the wall of the intestine. After moderate doses of the alkaloid the muscular tissue retains its irritability, and hence contracts after direct stimulation, without, however, true peristalsis showing itself. If the movements of the intestine be due from the outset to a direct stimulus of the muscle, the action of atropine remains more or less absent. At times we even observe after small doses a slight increase of peristalsis, so that atropine possibly at first stimulates the muscular tissue to a moderate degree. After very large doses the muscular irritability experiences a very notable diminution.

Muscarine, pilocarpine, and nicotine have no action upon the atropinised intestine, but physostigmine evokes active peristalsis or even violent tetanic contractions in it.

From these facts we may conclude that atropine destroys the irritability of certain nervous elements situated in the intestinal wall, probably ganglion cells, upon which the regular movements of the intestine depend. The effects of the atropine upon the muscular tissue play only a subordinate part in the poisoning of the animal as a whole.

In the rest of the organs which have smooth muscular fibres, that is, the *stomach, spleen, urinary bladder, and uterus*, the action of atropine only shows itself clearly when these organs are in a state of spasmodic contraction, as occurs especially in poisoning by muscarine or pilocarpine. Atropine brings about perfect relaxation in such cases, while physostigmine restores the spasmodic contractions again.

No other peripheral areas are influenced by atropine directly. A stimulation of the termination of the sensory nerves, just as after veratrine and aconitine, has been asserted by some observers to exist (Bouchardat and Stuart Cooper), and been denied by others (Fleming). Directly after the instillation of atropine into the eye of a cat a great increase may be seen in the secretion of saliva, and this is probably dependent upon the reflex effect of a sensory stimulus.

All these *actions of atropine* upon the peripheral organs might be rationally made use of in therapeutics if it were only possible to bring them about separately and with certainty in the organs which we wish to influence, as in the case of the eye, and if it were possible to keep them up for a prolonged period in any desired degree. As a matter of fact, however, the effects occur more or less simultaneously on all the organs, or upon those first of all in which we wish them least: thus, for example, there is the acceleration of the pulse, which is not only troublesome, but even under some conditions dangerous. Perhaps it will be possible to produce tropeïnes which in human beings cause exclusively, or at any rate mainly, one or other only of these effects.

By skilful manipulation, however, beneficial effects may be attained by means of atropine and extract of belladonna. In many cases *salivation* and *profuse perspiration* may be suppressed; in other cases these remedies exert no influence upon such morbid symptoms, probably because in the latter case the cause of the hyper-secretion lies in an affection of the glandular tissue, for to this the action of the atropine does not extend.

The inhalation of solutions of atropine as a spray may help to lessen the *increased acute secretion of mucus by the bronchi*, and so to moderate the cough. Perhaps concurrent spasmodic states in these organs are removed.

It has also been observed that *obstinate constipation*, which yields to no aperient, can at times be quickly and certainly removed when extract of belladonna is taken internally. There are probably cases in which, as in lead colic, the retention of the fœcal masses is caused by spasmodic constriction of separate portions of the intestine. Moderate doses of atropine are able to remove the spasm, without rendering impossible those movements of the intestine which are necessary for the removal of the fæces.

The importance of employing extract of belladonna instead of pure atropine is to be judged of in the same way as with extract of nux vomica and opium.

The most difficult task would probably be to find a satisfactory means of using atropine for the purpose of removing *spasmodic contractions* of the *uterus* with some degree of certainty by means of a purely *local action* of the drug upon it. Its very action upon this organ has not been sufficiently cleared up.

Finally, it is quite possible to conceive that an immoderate tonus of the *cardiac inhibitory fibres of the vagus* can be lowered when it is causing a dangerous retardation of the pulse in the course of cerebral and other affections. For the present we are not in a position to point out any tropeïne adapted for these purposes.

The *effects of the tropeïnes upon the central nervous system* in man are best seen in the case of atropine, and to a certain degree in that of hyoscyamine.

In frogs, after atropine there results general paralysis, and, in consequence of this, cessation of the voluntary and reflex movements followed by violent convulsions (Fraser). This is true also of belladonna, benzoyl tropine, and of a substance found in the hyoscyamus plant and not fully investigated, but called sikeranine (Buchheim), as well as of duboisine (S. Ringer and Murrell), but these do not occur after amorphous and crystallised hyoscyamine (Hellman, Harnack) and after tropine. These facts speak against the identity of duboisine and hyoscyamine.

The *cerebral symptoms* in man consist mainly in exhilaration of the mental functions, giddiness, restlessness, and automatic chorea-like movements, in continual, loud, disconnected talking, delirium, madness, raving (phantasmata et mania of Dioscorides), risibility, less often weeping : these symptoms are in each case more or less perfectly pronounced, and are accompanied by those symptoms which are dependent upon the local action. With these manifestations are associated disturbances of the visual power which are not entirely referable to dilatation of the pupils and to the paralysis of accommodation. Then there follows gradually the paralytic stage, with drowsiness, stupor, delirium, coma, and more or less violent convulsions.

The redness of the skin, resembling scarlet fever, so often observed, especially in the upper part of the body, and the similar colour with turgescence of the features, are probably connected with increase of the frequency of the pulse, with the increase of the blood-pressure caused thereby, and with the simultaneous dilatation of the vessels of the skin. Perhaps it is a case of a local action upon the latter.

Effect of atropine taken internally on man, according to Michea, Schroff, and Meuriot.

½ – 1 mg. (1/120 to 1/60 grain) : dryness of the mouth, frequently accompanied by thirst.

2 mg. (1/30 grain) : pupils dilated and inclined to be motionless, acceleration of the pulse, which in many cases is preceded by slowing of it (Lichtenfels and Fröhlich Schroff).

3 to 5 mg. (1/20 to 1/12 grain) : headache, dryness of the mouth and throat, difficulty of swallowing, alteration in the voice, even to aphonia (Michea), dryness of the skin, faintness, stumbling walk, excitement, restlessness, hasty movements (Schroff).

7 mg. (1/9 grain) : a very perceptible dilatation of the pupil, disturbance of vision (Michea).

8 mg. (1/8 of a grain) : an intoxicated condition, inability to stand straight, staggering walk. After still larger doses difficulty of micturition and diminution in the sensitiveness of the skin (Michea).

10 mg. (1/6 grain) : apathy, disturbance of consciousness, or even absence of it, hallucinations, delirium (Michea).

Hyoscyamine acts upon the *brain* somewhat differently from atropine. In men, after the administration of the amorphous modification, the raging delirium is as a rule not present, but after even small doses a hankering after rest and sleep predominates (v. Schroff). Even after subcutaneous injections of 5 to 10 mg. (1/12 – 1/6 grain) of crystalline hyoscyamine, sleep comes on along with acceleration of the pulse (Gnauck and Kronecker).

The general indication for the employment of these effects of atropine is the presence of *paralytic states of the brain*, yet no good is to be expected in cases of paralysis of the respiratory and vasomotor centres, and therefore not in ordinary collapse. On the other hand, we can succeed in counteracting either one or other of the systems of paralysis of the brain, or at any rate in moderating them, in cases of poisoning by morphine, for which atropine has been most employed as well as in nervous and mental diseases. Success depends upon the nature of the case in question, and consequently we cannot in general predict it for the individual cases. The empirical results obtained up to the present are full of contradictions, because in fact there are no definite indications to guide us in administering it empirically.

The Muscarine Group.

Muscarine is an alkaloid contained in the fly agaric (*Agaricus muscarius*). It causes a high degree of *irritation* in those peripheral organs which become paralysed by atropine. This is so powerful in the case of the inhibitory part of the *frog's heart*, that a perfect and lasting diastolic stoppage of the latter comes on, provided, however, that the cardiac muscle itself is not in a state of irritation, and that the pulsations are originating from the motor ganglia. In the case of mammals the following symptoms are caused in the various organs when their corresponding nerve elements are stimulated; slowing of the pulse, sinking of the blood-pressure, salivation, lachrymation, increase of the pancreatic secretion, as well as that of the liver and mucous and sweat glands, contraction of the pupil, and spasm of the accommodation, violent tetanic contractions of the stomach and intestinal canal, with the consequent diarrhœa and vomiting; finally, contraction of the bladder, of the spleen, and probably also of the uterus.

All these symptoms, and also the stoppage of the heart in the frog, disappear entirely under the influence of a corresponding dose of atropine, and, on the other hand, they never appear at all in the case of an animal which has been atropinised, provided that the action of the atropine has reached the requisite degree. If after small doses of atropine the irritability has not been quite removed but merely lowered, large doses of muscarine are still able to exert some influence.

Mammals die after poisoning by muscarine in consequence of the stoppage of the heart. The danger can be quickly and safely removed by small doses of atropine; consequently the latter can also be of great service in the treatment of poisoning by fly agaric.

The subcutaneous injection of 1 to 3 mg. ($\frac{1}{60}-\frac{1}{20}$ grain) of muscarine causes *in man* profuse salivation, rush of the blood to the head, and increase in the frequency of the pulse, which also, in the case of dogs, precedes slowing of it, flushing of the face, giddiness, oppression, anxiety, nausea, griping and rumbling in the belly, disturbance of vision, especially spasm of the accommodation, copious perspiration on the face, and to a less degree on the rest of the body.

Of these effects the first to come on are the salivation and a moderate degree of perspiration. Muscarine might therefore be employed therapeutically in cases similar to those in which pilocarpine is used.

THE PILOCARPINE AND NICOTINE GROUP.

The two alkaloids, *pilocarpine and nicotine*, act as stimulants of the same organs as muscarine, but, at any rate in the case of the heart, the points attacked are different; and besides this, after the irritation, there results a paralysis of the terminations of the inhibitory fibres.

The heart of the frog is at first brought to a state of diastolic standstill, just as after muscarine; and the access of this can be prevented by atropine. This standstill is transitory, and as soon as the rate of the heart's beat has again reached its maximum, stimulation of the vagus is no longer able to cause the diastolic standstill of the heart, or even a slowing of its beats; yet muscarine and stimulation of the sinus act just as in the case of the normal heart, and can only be rendered inert by atropine. Paralysis of the fibres of the vagus is no more caused by pilocarpine and nicotine than by any other poison. The parts of the inhibitory mechanism attacked by them consequently lie between the fibres proper and those parts upon which muscarine exerts an irritant and atropine a paralysing influence. Large doses of pilocarpine ultimately paralyse the heart itself.

In the eye the two alkaloids act just as muscarine, but after the contraction of the pupil there follows a *moderate degree of dilatation*, so that, just as in the case of the termination of the vagus in the heart, the original stimulation of the terminations of the oculomotorius is followed by a decrease in its irritability.

As regards the *glands* and *abdominal organs*, only the irritation is distinctly to be seen.

The increase of all the secretions, especially of the secretion of the sweat and saliva, and the violent contraction of the *stomach* and *intestinal canal*, which culminate in vomiting and diarrhœa, are the most prominent signs of this action. These also are easily removed by atropine.

Nicotine in large doses rapidly brings about paralysis of all parts of the central nervous system, and especially of the respiratory centre. Hence death results with the symptoms of collapse, almost always preceded by convulsions. Even small doses, say $\frac{1}{4}-\frac{1}{2}$ mg. per kg. ($\frac{1}{580}-\frac{1}{250}$ grain per lb.), cause in mammals and in man similar indications of collapse that is, a slight degree of paralysis of the central nervous system; but these, however, are not fatal. Especially prominent therewith is the general weakness which, along with the symptoms on the part of the peripheral organs, particularly nausea and vomiting, give the distinctive appearance to the poisoning which is so often observed in the case of those learning to smoke. In

URETHAN, PILOCARPINE, ATROPINE, CHLORAL, HELLEBOREÏN (DOG).

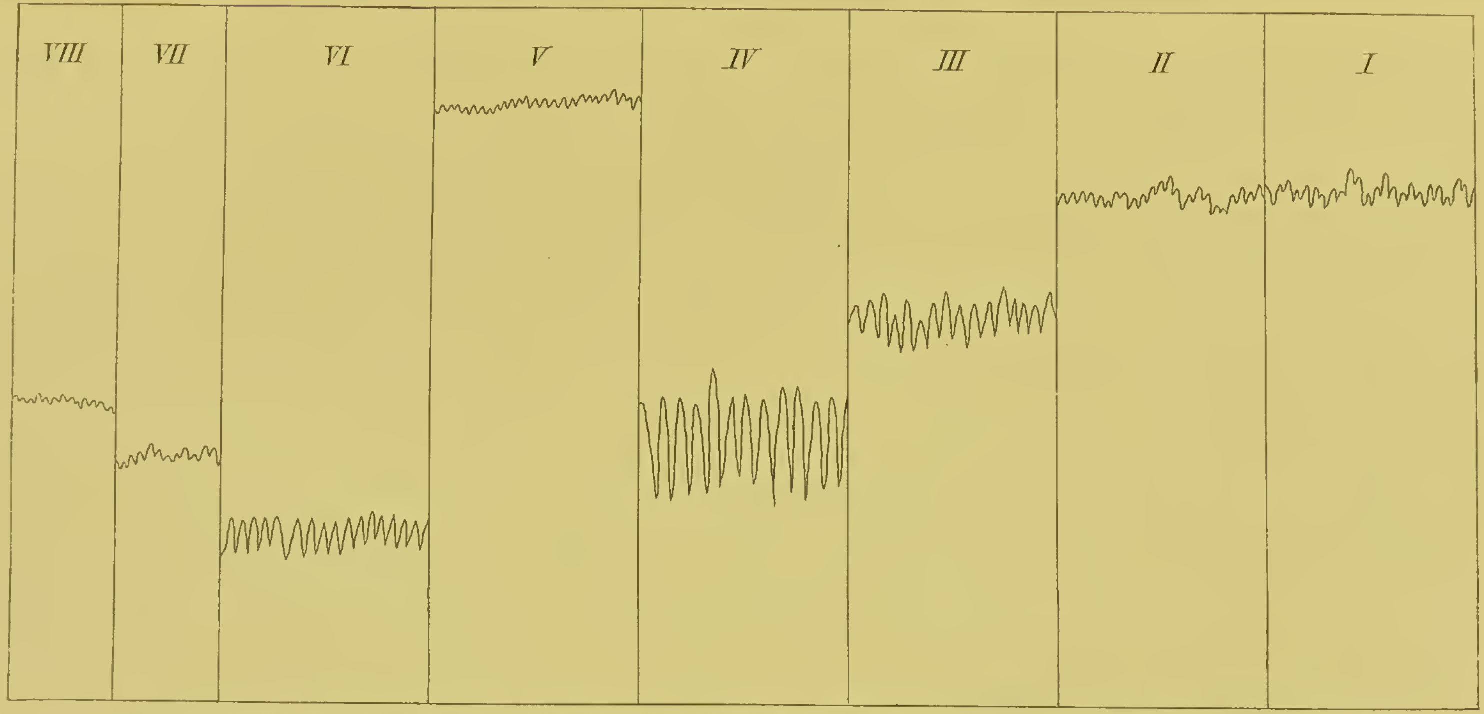


FIG. 4.—Curve showing the relationship existing between various substances which influence the blood-pressure, and which were consecutively injected.

I. Animal normal, blood-pressure 126; pulse 28 in 10 seconds.
II. *Urethan* injected: Pulse and blood-pressure unaltered.
III. *Pilocarpine*; blood-pressure lowered to 96; pulse 19.
IV. Further stage of the action of Pilocarpine; blood-pressure 70.
V. *Atropine*; sudden rise of blood-pressure from below normal to 145, pulse 30.
VI. Deep *Chloral Narcosis*; blood-pressure has fallen to 50, pulse 20.
VII. and VIII. Show the steady rise of the blood-pressure under *Helleboreïn*; pulse becoming more frequent.

addition to this, nicotine causes in frogs irritation of the terminations of the motor nerves, and then, after the manner of curara, paralysis of them.

Indeed, by means of properly regulated doses of nicotine, it is possible to cause in man certain of the actions upon the above-mentioned peripheral organs, more particularly salivation and increased peristalsis of the intestine, without producing simultaneous symptoms of paralysis of the central nervous system. This is of occasional occurrence, especially after the administration of *clysters of tobacco.* This method of giving nicotine or tobacco is always fraught with a certain amount of risk, and consequently should be set aside.

Pilocarpine causes disturbances of the functions of the central nervous system similar to those resulting from nicotine, especially dyspnœa, spasmodic twitching and trembling of the body, and rotatory movements. In frogs it causes well-marked convulsions and indications of paralysis; after large doses (10 – 15 mg., $\frac{1}{6}$ – $\frac{1}{4}$ grain) the latter come on at once. In mammals the lowering of the tonus of the vascular nerves shows itself very distinctly.

But all these effects offer no hindrance to the employment of pilocarpine, when it is a question of *causing copious perspiration and salivation*, because they only come on after larger doses than are required for therapeutic purposes. In man special dangers in fact do not claim our attention, because, as the dose is raised, along with the first symptoms of the action of pilocarpine—that is, the salivation and perspiration—symptoms on the part of the stomach and intestine appear, in other words vomiting and diarrhœa, and these indicate the degree of action with which the further employment of larger doses of the remedy should cease. All this takes place long before the occurrence of those threatening symptoms which depend mainly upon the paralysis of the vascular nerves and of the heart.

Pilocarpine may also be employed for the purpose of increasing the secretions in general, more particularly *the saliva and perspiration.* Although we have not sufficient facts as to the behaviour of the urinary secretion, yet it may be stated with sufficient certainty that it is not directly influenced by pilocarpine. *The employment of* *this remedy in renal diseases* can only be with the idea of removing by other paths, such as the skin, the water which passes away by the kidneys as a rule. To what extent we are justified in expecting therapeutic success, clinical experience alone can tell, and this at present is too recent, and is not sufficiently extensive, to permit us to attempt a correct decision. Moreover, not even a theoretical answer can be given to the question as to what cases might be benefited by increasing the salivation, and especially the perspiration, through the influence of the nerves: this can only be answered upon the basis of clinical experience, yet it may be taken for granted, judging from the nature of the action of pilocarpine, *that the therapeutic value of the remedy is entirely dependent upon the consequences of the increased activity of the secretions.* Hence it is much valued as a powerful absorbent for the removal of exudations, even when these are situated in the eye. On the other hand, it is contra-indicated in those cases in which the increase of these secretions is to be avoided. Moreover, we must not lose sight of the facts that the bronchial secretion is increased; that rabbits, in poisoning by this substance, not infrequently die from *œdema* of the lung, and that predisposition to the latter may contra-indicate the employment of the remedy in man. Here foresight must be used before ill results thrust it on us.

It must be noticed that pilocarpine often contains some *jaborine*, a basic decomposition product of pilocarpine; and since this substance acts like atropine, it may partially or even entirely *prevent the action* of the latter alkaloid.

THE CONINE AND LOBELINE GROUP.

To the alkaloids of the previous group *conine* and *lobeline* are closely related. The former is an alkaloid which contains no oxygen, is fluid and volatile, and which yields beautifully crystalline salts with hydrochloric and hydrobromic acids. It causes from the outset paralysis of those parts of the inhibitory apparatus of the heart, which, as already described, are first stimulated and then paralysed by nicotine and pilocarpine.

Lobeline has not yet been closely investigated chemically, but it acts upon the inhibitory apparatus after the manner of atropine.

Conine increases the secretion of the tears, saliva, and urine (Prevost), but the behaviour of the rest of the glands is unknown.

Whether the peristaltic movements of the intestine experience an increase, has not been specially investigated, but the occurrence of vomiting and diarrhœa among the symptoms of poisoning points to an action like that of nicotine.

The peripheral organs behave in the same way towards *lobeline.* Doses of 2 – 10 mg. pro kg. ($\frac{1}{60}$ – $\frac{1}{12}$ grain per pound) of an animal cause salivation, vomiting, and diarrhœa (Rönnberg).

Both alkaloids *paralyse the central nervous system*, and, especially in frogs, they act like curarine upon the ends of the motor nerves.

Conine induces at the same time violent *convulsions*, but only in frogs, when the motor nerves have been protected from the action of the poison by ligature of the vessels (Harnack and Meyer). Others have stated that the spasms are absent even under these conditions (Fliess and Kronecker).

Lobeline appears primarily to act as a *narcotic* upon the brain, and to bring about drowsiness and insensibility to cutaneous stimuli. In *man*, after 11 mg. ($\frac{1}{6}$ grain), administered in several small doses, there were observed a feeling of rawness of the throat, colicky pains, nausea, pultaceous stools, and a slight degree of drowsiness (Rönnberg). After taking the official tincture of lobelia, these symptoms have been observed to occur in a more pronounced degree in the form of a burning sensation in the throat—dysphagia, vomiting, a feeling of constriction of the trachea and chest, and along with this diaphoresis, contraction of the pupil, lethargy, and other intense cerebral symptoms.

Whether some of these symptoms are dependent on special effects upon central or peripheral portions of the nerves of the respiratory organs, and whether from these an indication be deducible for the employment of lobeline or of the official preparations of the lobelia plant in the various forms of asthma, cannot as yet be decided. The opinions as to its success are not so favourable in Europe as in America.

The employment of conine, especially in spasmodic affections, is not based either upon rational or empirical indications. The use of it has been entirely handed down to us by tradition.

THE PHYSOSTIGMINE GROUP.

The alkaloid *physostigmine*, contained in the Calabar bean, causes stimulation or irritation of the striped and unstriped muscles, and at the same time paralysis of every area in the central nervous system. Harnack and Witkowski have investigated this alkaloid after its purification from calabarine, a substance which acts like strychnine.

The *stimulation of the voluntary* muscles shows itself in mammals, and at times in frogs, in the form of fibrillar twitchings, which continue after section of the afferent trunks of the nerves as well as during complete chloral narcosis, and careful though perfect curarization. If the curarization be too strong, they cease almost certainly because of the lowering of the muscular irritability. In frogs, when the muscles have first been poisoned with curara, then with physostigmine, their sensitiveness increases for stimulation with the opening secondary shock, and that without their working power being augmented.

Through this influence upon the muscles, it results that *the heart* contracts more powerfully, and this causes *an increase of the blood-pressure*, even if beforehand atropine, curara, or chloral hydrate has been given. From this we must conclude that the rise of blood-pressure is neither dependent on paralysis of the inhibitory apparatus, nor exclusively upon a narrowing of the vessels. The rise of blood-pressure is accompanied by slowing of the pulse. This, however, does not occur in animals which have been chloralised before being poisoned.

The diastolic stoppage of the frog's heart, caused by muscarine, may be so far removed by means of physostigmine, that regular contractions take place ; yet it may easily be seen from the nature of the beat that the action of muscarine still continues, and is only being overcome by irritation of the cardiac muscle itself. Stimulation, too, of the vagus and sinus no longer causes stoppage of the heart. The latter, however, does come on if, after giving muscarine and physostigmine, we reduce the irritability of the cardiac muscle, and consequently set aside the action of physostigmine, by means of small quantities of a muscle-paralysing substance, *e.g.*, apomorphine, or neutral solutions of oxide of copper. Finally, atropine can remove this stoppage of the heart, provided the muscular tissue be still sufficiently irritable.

Various other substances besides physostigmine can start the heart into action again after it has been brought to rest through muscarine. To these belong camphor, monobromide of camphor, borneol, sulphate of aniline, arnica-camphor, cumarine, and guanidine. The last probably stimulates not only the muscles but the motor ganglia in the heart.

The irritation of the involuntary muscle fibres of the intestine causes peristaltic movements, which may increase to the most violent spasm, and it induces contraction of the stomach, of the spleen, of the bladder, and of the uterus, and none of these effects are influenced by doses of atropine sufficient to paralyse the nerves.

If muscarine, atropine, and physostigmine be judiciously administered to an animal in succession (in cats about 5 mg. [$\frac{1}{12}$ grain] of the latter), there may be seen, especially well in the intestines, at first a spasm, then perfect relaxation, and finally through the latter poison a fresh spasm come on.

The symptoms of these actions on the part of physostigmine are retching, vomiting, diarrhœa, and micturition.

The same sequence of corresponding changes can be brought about in the eye by these three poisons—that is to say, first, contractions of the pupil through muscarine with spasm of the accommodation, then dilatation of the former and paralysis of the latter through atropine, and finally contraction again and spasms through physostigmine.

Physostigmine makes the atropinised pupil narrower, because it stimulates the muscles of the iris, for these are not paralysed by moderate doses of atropine. The latter, as a rule, dilates the pupil which has been made narrower under physostigmine, because, after the application of the alkaloid, the size of the pupil is dependent partly upon the direct irritation of the sphincter by the poison, and partly on the usual tonus of the oculo-motorius. The latter is removed by atropine, and hence there results dilatation.

Since physostigmine stimulates simultaneously the sphincter and the dilator in the iris, which act one against the other, it is impossible by this myotic to contract the pupil, even of cats, so much that the margin of the iris comes in contact, as is the case under muscarine.

It is impossible to explain the increase in the secretion of the glands, the increase of the mucus, saliva, tears, and perspiration, caused by physostigmine. It might easily be imagined to be merely a case of direct irritation of the gland cells. The fact that even in the atropinised maxillary gland salivation occurs after physostigmine is given, is in harmony with this view, but it cannot explain the observation that extract of Calabar bean makes the terminations of the salivary nerves irritable again after they have been paralysed by atropine (Heidenhain).

Every part of the central nervous system is paralysed very rapidly by physostigmine, and death comes on in consequence of the stoppage of the respiration, with symptoms of acute suffocation. In many kinds of animals, especially cats, a high degree of irritation precedes the general paralysis, and this irritation shows itself in their running impetuously backwards and forwards, presumably because of the violent dyspnœa. The fatal doses amount on an average to 0·5 – 1 mg. pro kg. ($\frac{1}{240}$ – $\frac{1}{120}$ grain per lb.) of a mammal. In guinea-pigs predisposed to epileptic convulsions in consequence of Brown-Sequard's or Westphal's operation, these attacks come on with unusual frequency during the first few days after moderate poisoning with physostigmine (Harnack and Witkowski). Accordingly, there is little hope of doing much good by means of physostigmine in treating diseases of the central nervous system in which spasms or spasmodic symptoms occur. And this is quite apart from the fact that such treatment is always associated with the great risk that symptoms of collapse come on so soon as really efficient doses are given. Consequently the empirical results have turned out correspondingly unfavourable. Attempts to employ this substance in therapeutics are much less frequent now than formerly.

Of the actions of physostigmine upon peripheral organs, that upon the eye is the only one that can be evoked without any danger at all. Its importance consists only in the contraction of the pupil and in the spasm of accommodation which may be made use of in paralytic conditions of the parts affected, somewhat after the fashion of a "gymnastic" remedy. But the muscles of the blood-vessels in the interior of the eye are stimulated, and they become, as a consequence, narrower, and quite a new condition in the circulation of the eye follows; this may exercise the greatest influence upon the nutritive processes in the latter. The immediate result is the reduction of the intraocular pressure. The favourable results first observed by Laqueur in the treatment of acute glaucoma must be considered to be dependent upon this action on the vessels. Pilocarpine and muscarine are useless for this purpose, for they have no influence upon the vessels. Moreover, for the purpose of contracting the pupil, physostigmine is much better adapted than either of the other alkaloids, seeing that its action lasts longer.

A trifling contamination with calabarine does not in any way prejudice the employment of physostigmine in ophthalmic practice. Impure physostigmine is now and then made use of under the name of eserine. Although the solution of physostigmine becomes red and afterwards brown, it does not appreciably lose its strength.

THE APOMORPHINE GROUP.

Apomorphine is a substance obtained from morphine, through the abstraction of water by the action of concentrated mineral acids. It causes in mammals, at first, great irritation, and then paralysis of the motor and sensory centres in the brain and medulla oblongata. In frogs the irritability of the muscles is lessened after doses of 0·5 to 5·0 mg. ($\frac{1}{120} - \frac{1}{12}$ grain); after 10 mg. ($\frac{1}{6}$ grain) it becomes totally annihilated, and rigidity does not come on after death. The cardiac muscle behaves in a similar manner. In mammals this action upon the muscles cannot with certainty be demonstrated, and the alterations in the functions of the brain and medulla exclusively predominate; this is shown by symptoms of irritation, especially in the case of rabbits: the latter exhibit, after 5 to 10 mg. ($\frac{1}{12} - \frac{1}{6}$ grain), very great restlessness, excitement, and terror, especially when their senses are in any way influenced, as by handling them or by making a noise. Along with this, a strong impulse to spontaneous movement begins to show itself, and this causes the animal to run incessantly backwards and forwards, to jump against the wall, and to gnaw any objects which it comes near.

Death results in these animals after 10 to 20 mg. ($\frac{1}{6}$–$\frac{1}{3}$ grain), and is due to suffocation, for the respiratory centre succumbs to paralysis, preceded by irritation indicated by the rise in the frequency of the breathing. Death is preceded by symptoms of paralysis, and by violent convulsions, which latter come on before the disturbances of the respiration have advanced so far as to justify the idea that they are chiefly due to suffocation.

Similar states of irritation are observed in cats and dogs, but in the case of the latter the convulsions only occur after the injection of 0·5 to 0·6 g. (7 or 8 grains) of apomorphine into the blood.

One solitary symptom—viz., vomiting—however, shows itself after doses of apomorphine far less than are necessary to cause any of the above results or their consequences. This comes on with all its characteristic concomitant symptoms quite regularly in man or any other animal which is at all subject to this process.

In dogs vomiting follows the subcutaneous injection of 0·5 to 1·0 mg. ($\frac{1}{120} - \frac{1}{60}$ grain) of hydrochlorate of apomorphine, and that within two to three minutes; in adults after 5 to 10 mg. ($\frac{1}{12} - \frac{1}{6}$ grain) it is seldom longer than a quarter of an hour in coming on, but with children in the earlier years of life 0·5 to 2·0 mg. ($\frac{1}{120} - \frac{1}{30}$ grain) is sufficient.

The access of vomiting is preceded by that set of symptoms which is characteristic of nausea, that is, qualmishness, a feeling of exhaustion and languor, weakness of the muscular power, a feeling of impending perspiration or a slight feeling of warmth, increased secretion of saliva, and we may also say of mucus, and immediately before the vomiting a great acceleration of the pulse. After doses which cause vomiting rapidly, these symptoms may be more or less wanting. Smaller doses, insufficient to cause vomiting, induce a persistent qualmishness, a feeling of languor, increase of the secretions and slowing of the pulse.

Small doses of emetics of every kind are used as so-called expectorants in diseases of the lungs, and especially in bronchial catarrh, for the purpose of easing the removal of the tough mucus by coughing and hawking. In this way the impulse to cough is alleviated, and that quiet is procured which is necessary to the cure of the morbid mucous membrane. This expectorant action is, at all events, closely connected with the increase of the secretions, which comes on during the nausea, and probably with the secretion of mucus. How this and the remaining symptoms of this stage, and of actual vomiting, are to be explained, cannot here be further entered into. Certain it is, that it is not a question of the direct action of the emetic.

The very striking rise in the frequency of the pulse which, especially in dogs, precedes the vomiting, must be considered as dependent upon stimulation of the pulse-accelerating nerves, brought about by the act of vomiting, because in this, just as when these nerves are stimulated by other means, the increase in the number of beats is not accompanied by any alteration of the blood-pressure.

That the vomiting after apomorphine owes its origin to the irritation of the central areas may certainly be taken for granted. It is the earliest—we might say the gentlest—of the degrees of irritation, which subsequently affect more extended areas of the central nervous system. In this one is reminded of the fact that the reflex stimulus which results when the palate is tickled causes vomiting, while energetic attacks upon this region of the throat often have no effect.

As an emetic apomorphine is decidedly to be preferred to tartar emetic, emetine, ipecacuanha, and even sulphate of copper, because it can be employed subcutaneously without inducing inflammation at the point of injection, as the substances mentioned so readily do. Moreover, the action comes on very rapidly, and that, too, after relatively small doses, while the dangerous symptoms occur only after far larger ones.

To enter into the therapeutic importance of vomiting or its rationale, is not the duty of pharmacology. Just as in other cases, the nausea and vomiting brought about by apomorphine may have evil consequences, which consist, especially in children, in a state of collapse, the remedy itself is not to be blamed for this issue. It is in the highest degree improbable that a direct action upon the muscles is at work here.

Although a solution of apomorphine rapidly becomes green and then almost black, it does not materially lose its efficiency.

The Emetine Group.

Emetine is an alkaloid contained in ipecacuanha, which does not yield any distinctly crystalline salts (Podwyssotzki), being itself only with difficulty crystallisable; although colourless, it becomes yellow when exposed to the light. Doses of 0·01 g. ($\frac{1}{6}$ grain) in frogs paralyse the central nervous system, and lessen the working power of the muscles without destroying the irritability of the latter before death.

Small doses of 0·005 to 0·01 g. ($\frac{1}{12} - \frac{1}{6}$ grain) cause at first irregularity in the rhythm and contraction of the ventricle of the frog's heart, and finally lead to a stoppage of the latter in the relaxed—that is, the diastolic—state, with loss of irritability; yet after these doses recovery of the animal may still take place.

In mammals, especially dogs, no matter how the substance be given, violent intestinal symptoms are gradually developed, consisting of simple or bloody stools, with tumefaction, reddening, and ecchymosis of the mucous membrane, just as we find in poisoning with arsenic, platinum, antimony, and iron, also with sepsin. The lungs are frequently found, especially in rabbits (Duckworth), in a high condition of congestion, œdematous infiltration, and red hepatisation.

After injection, subcutaneously or intravenously, death results through paralysis of the heart. In cats the dose in the former case is about 0·09 to 0·1 g. ($1\frac{1}{3}$ – $1\frac{1}{2}$ grain); in the latter 0·02 to 0·05 g. ($\frac{1}{3}$ – $\frac{3}{4}$ grain). Before the paralysis of the heart sets in, the blood-pressure sinks almost down to nothing, while, as after chloral hydrate, the individual pulsations rise as high as 50 or 60 mm. ($1\frac{1}{2}$ inch or more) above the abscissa (Podwyssotzki).

Moreover, the vascular system is paralysed sooner than the heart, just in the same way as is observed in the above cases of poisoning in which the same intestinal symptoms occur.

Emetine is also a direct irritant. After subcutaneous injection it induces abscesses, and when applied as an ointment to the skin it causes pustules, and, brought into contact with the mucous membranes, it causes irritation and inflammation, as, for instance, when the dust of ipecacuanha gets to the conjunctiva and the bronchial mucous membrane. The intestinal symptoms are not dependent upon these effects, because they occur after every method of administration.

The main symptom of the action of emetine is, from a practical point of view, the vomiting, which comes on, as a rule, earlier than the other effects, just as in the case of apomorphine. At times diarrhœa comes on simultaneously.

Nothing certain is known about the origin of vomiting. The idea that it is brought about reflexly through peripheral irritation of the centripetal nerves of the digestive organs has just as much to be said for it as the idea that emetine stimulates the centrally situated parts, or, in other words, a centre for vomiting.

The nauseant stage is exactly like that of apomorphine. As an expectorant, emetine, in the form of ipecacuanha, may be preferable to apomorphine, because it is more slowly absorbed, and consequently the action can be more easily and uniformly kept up for a considerable space of time.

In past times, more frequently than is the case now, ipecacuanha was employed in nauseant and emetic doses in affections of the stomach and intestine of the most various kinds, including amongst these diarrhœa, and especially dysentery. That vomiting can be in such cases occasionally of use, through its emptying the stomach, is intelligible enough, only nowadays it is frequently replaced by the œsophageal tube and stomach pump. As regards small doses, there is need of a thorough critical examination of the question whether emetine or ipecacuanha exercises a favourable influence in diseases of the stomach and intestine, and if so, what are the cases in which it does so. Only then can an explanation of this influence be attempted. Meanwhile the statements relative to this are far too contradictory.

THE SAPONINS.

Next to the emetine group come those substances which contain the so-called saponins. To these belong senega and sarsaparilla. The saponins are crystalline or amorphous glucosides, found widely distributed through the vegetable kingdom: they are all, with but few exceptions, very soluble in water, and render it frothy.

According to recent researches, the most active substances in these drugs are the sapotoxin and the quillaïn or quillaïc acid, found in saponaria and quillaia (Kobert).

The "saponinum purum" made from the acetyl compound by Stutz and Geuther is absolutely inert. By treating the above-mentioned principles with alkalies they lose their active properties.

The other saponins, as digitonin (in digitalis), smilacin or parillin (in sarsaparilla), cyclamin (in cyclamen), primulin (in primula) are pharmacologically less active than the principles derived from quillaia.

Their action is related to that of emetine; it is probable that there would be almost no difference if the saponins were only as readily absorbed as the latter. They are, however, almost unabsorbable from the subcutaneous tissue, and hence only slowly induce general actions upon the system, but they cause a violent local one, consisting in phlegmonous inflammation. From the intestine they are absorbed only when it is inflamed or ulcerated. Injected into the blood, sapotoxin and quillaïn cause paralysis of the central nervous system, and in dogs a very characteristic affection of the intestines, consisting in effusions of blood starting from the subserosa, and later extending all through the mucosa and submucosa.

Small doses cause symptoms in man closely resembling the nauseant stage of emesis; that is, a raw feeling in the throat, tendency to cough, and increased secretion of mucus. Hence we can employ those drugs which contain saponins with the same purpose as the emetics proper—for the expectorant action. The advantage of this drug, as compared with ipecacuanha, is to be found in the fact that through its great difficulty of absorption it is possible to sustain the gentlest degree of expectorant action for a long time without incurring any injurious effects. Consequently senega should be preferred to other expectorants in cases where the action must be kept up for a long time—for weeks, or even for months—and consequently in chronic affections, and with patients who cannot stand constitutional actions of other expectorants. Yet senega is by no means indispensable, seeing that with skilful management the same result may just as well be attained by means of ipecacuanha. In practice, however, it would be still better to employ quillaia bark (*Quillaia saponaria*) instead of the expensive, ill-tasting senega root, for, like the latter, it also contains the same principles, but in much greater quantities.

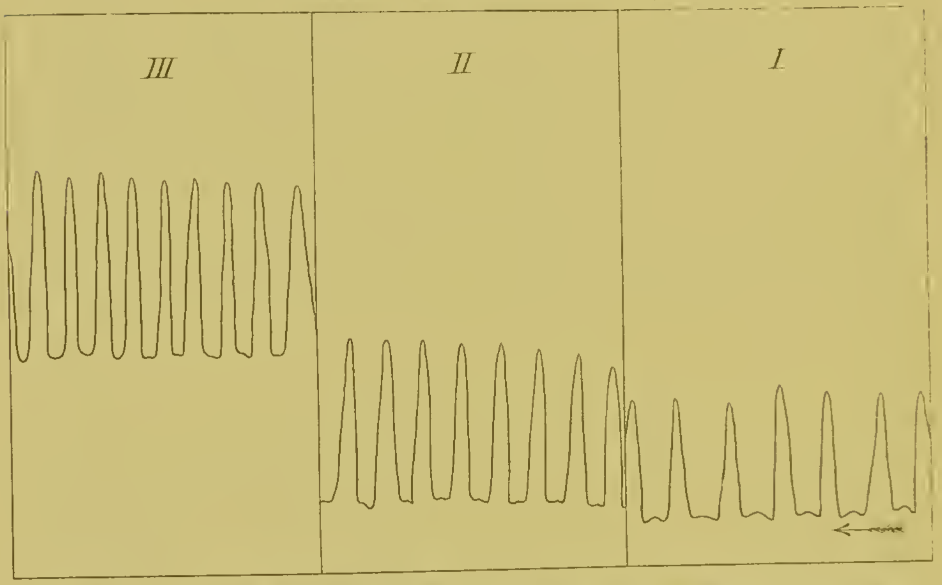
As regards the employment of sarsaparilla in the form of the celebrated Zittmann's decoction for the treatment of syphilis, Böcker more than a quarter of a century ago, after careful historical, critical, and experimental investigation, arrived at the opinion that " sarsaparilla may be an excellent remedy, but no one has yet proved it to be such." To-day we may be allowed to doubt the first part of the sentence, and unhesitatingly pronounce the opinion that sarsaparilla cannot possibly be an excellent remedy in syphilis as compared with similarly constituted drugs, *e.g.*, saponaria.

THE DIGITALIN GROUP.

A number of non-nitrogenous, neutral vegetable substances, of which the greater part belong to the glucosides, act in so uniform a manner upon the heart of all sorts of animals, leaving quantitative differences out of the question, that each of the substances seem, as regards this action, to be a true copy the one of the other.

The most important of these are digitalin, digitaleïn, and digitoxin, which are all constituents of digitalis; and next after these comes scillaïn, which is the active principle of the squill plant, and is found in commerce in a very impure state under the name of scillitoxin. Of the rest, the most important to mention are helleboreïn, which is very soluble in water, and occurs in the various species of hellebore; next, oleandrin, to which, as well as to digitalin (nereïn), the common oleander owes its poisonousness. Then there is apocynin, which occurs along with apocyneïn in Canadian hemp (*Apocynum cannabinum*); and, finally, there is adonidin, which is contained in the spring Adonis. The three last, as well as scillaïn, are not crystalline, and are almost insoluble in water. Convallamarin, from the lily of the valley, as well as digitaleïn and apocyneïn, are glucosides, which, like saponin, form frothy solutions with water. Other substances belonging to this group are but rarities, such as antiarin, strophanthin, and thevetin, while the remainder have either not been examined particularly, or have no special interest.

The action of these substances consists almost exclusively in the fact that they alter, in a peculiar way, the elasticity of the cardiac muscle, without at first modifying the contractility of it. The immediate effect of this alteration is seen in increase of the volume of the pulse, with prolongation of the diastole. At this stage of the action of digitalis, the absolute working power of the heart experiences neither an increase nor a decrease. On the other hand, the quantity of blood which, under these conditions, is driven into the aorta is



CHLORAL AND DIGITALIN.—(DOG.)

FIG. 5.—Curve showing the effect of digitalin in raising the blood-pressure after it has been lowered by chloral.

I. Deep chloral narcosis. Blood-pressure 40.
II. Result after injection of 7½ mg. digitalin into the blood. Blood-pressure 60.
III. Result after the injection of 5 mg. more. Blood-pressure 125.

greater than before, not only at every beat of the pulse, but even in a given unit of time, and consequently this is the case, though the number of the pulsations may have been diminished. These substances consequently bring about the better filling of the arteries, seeing that they magnify the relative efficiency of the heart. As a

DIGITALINE.—(CURARISED DOG.)

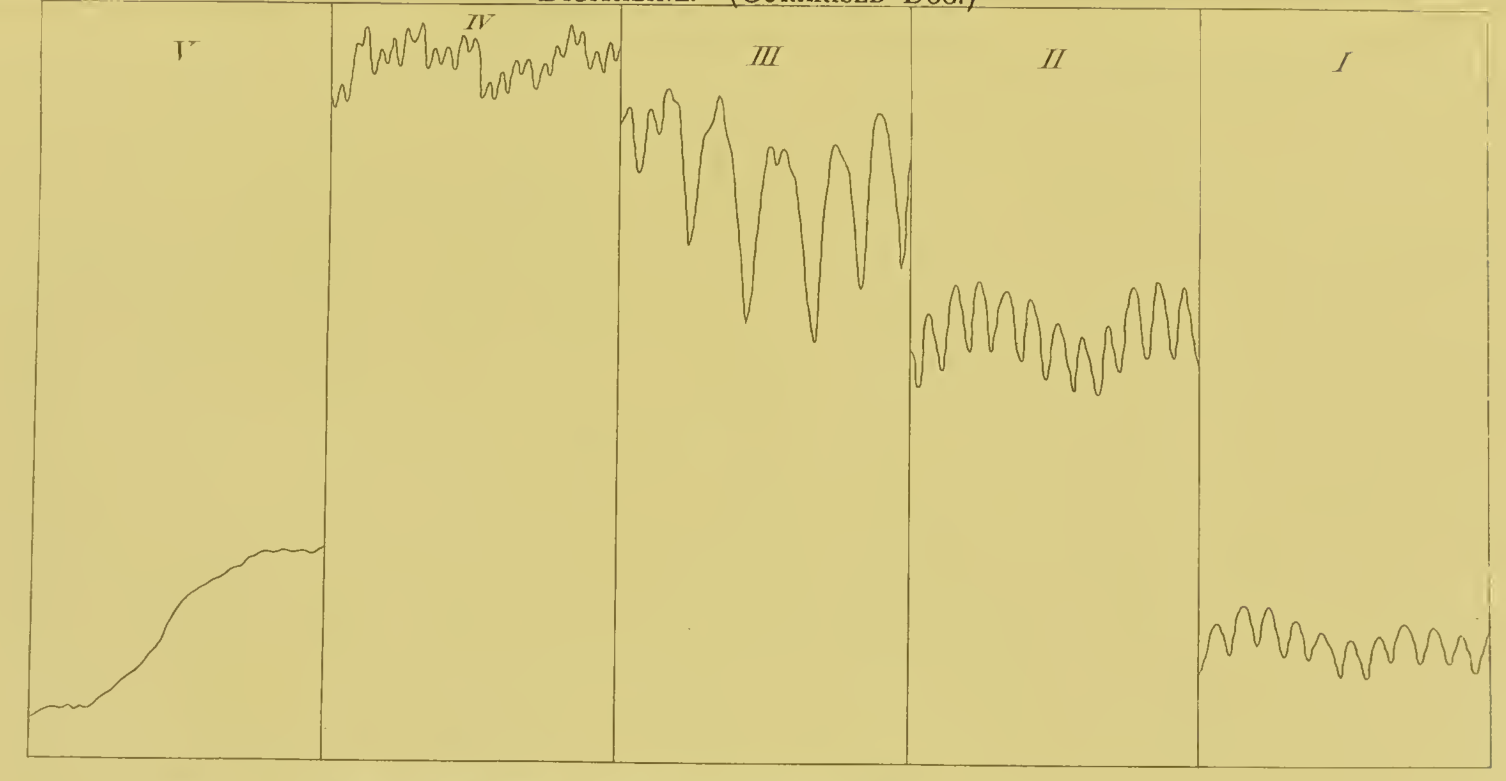


FIG. 6.—Curve showing the effect of digitaline upon blood-pressure.

I. Before the giving of the digitaline. Blood-pressure 86 ; pulse 21 in 10 secs.
II. Some time after the injection of 1 mg. Blood-pressure 150 ; pulse 22.
III. Further injection of digitaline. Blood-pressure 164 ; pulse 20.
IV. After further injection, total amount injected being 8·9 mg. Blood-pressure 210 ; pulse 40.
V. Fall of blood-pressure preceding death. The depth of the curve is 30 mm. reduced, corresponding to 60 mm. blood-pressure.

result, the blood-pressure becomes under all conditions increased, no matter whether it may have been relatively high beforehand or very low—as, for instance, in very deep chloral narcosis. Along with this increase of pressure, which we can indirectly prove to occur in man, there comes on slowing of the pulse, which depends upon stimulation of the inhibitory mechanism of the heart, a stimulation partly conveyed by the vagus, but partly also local. This slowing is absent if the inhibitory apparatus has been beforehand paralysed by atropine, and this latter paralysis has no effect upon the occurrence of the rise of pressure. In the course of a case of poisoning, the inhibitory terminations of the vagus lose their irritability even without atropine, and then can induce increase of the blood-pressure along with acceleration of the pulse.

The next stage of the action of digitalis is recognisable in the frog's heart, by peculiar irregular so-called peristaltic movements of the ventricle, and in mammals by continuous high blood-pressure, accompanied with irregularity both in the action of the heart and in the frequency of the pulse.

In the frog, a characteristic stoppage of the ventricle in systole alternately supervenes, and after a short time the auricles also come to rest.

In this condition, however, the heart is not yet paralysed ; for when it is put into a state of diastole by means of mechanical dilatation, energetic contractions occur, till, finally, a total loss of the irritability of the muscle comes about. Yet it still retains the power to return to a state of the most pronounced systole, so soon as the mechanical dilatation ceases. In mammals, naturally enough, this form of stoppage of the heart cannot be demonstrated. When, finally, the usually sudden arrest occurs, as indicated by the rapid fall of blood-pressure, the heart is at once paralysed, and the animal dies immediately.

Of these actions, the first stage—that is, the rise of blood-pressure, and the usually concurrent slowing of the pulse—can in man be brought about, and kept up even for a long time, by small doses of the substances of this group, and that without danger to life. To the raising of the blood-pressure alone can any essential therapeutic importance be ascribed. The remaining symptoms, and especially the slowing of the pulse, upon which so much stress is laid in the employment of digitalis, are either results of the high arterial pressure, or come on, like the inflammatory processes at the point of application, as merely occasional disturbing factors.

If better filling up of the arteries, and the consequent rise of arterial pressure, be the changes which one is able to cause by these substances in the healthy and the sick, then the indications for its rational employment follow of themselves. Wherever symptoms of illness are due to insufficient filling of the arteries, and to an abnormally low blood-pressure, these remedies can in certain cases be of use.

Valvular affections of the heart are among the chief of those diseases whose results and symptoms are to be considered mainly due to deficiency of blood in the arterial vessels, and to a too low pressure in them. They cause, first of all, stagnation of the blood in the veins and capillaries of the systemic and pulmonary circulations. This leads on, further, to diminution in the secretion of the urine, disturbances of respiration, and supervention of dropsy. If in these cases the blood-pressure be raised, the secretion of urine increases, the effused fluid becomes absorbed from the cavities and tissues of the body, and the disturbances of the respiration disappear.

This so-called diuretic action is only to be considered as a result of the increased blood-pressure. If the latter be already at its normal height, as a rule no increase in the excretion of urine is brought about by digitalis, evidently because it has already reached its maximum. When the action is at its height, the quantity of the urine may, in the case of animals, be even lessened (Brunton).

In what special cases an artificial raising of the blood-pressure is of use, it is the duty of practice of medicine to determine.

Since the heart, when under the influence of digitalis, is compelled to carry on a greater amount of work, the condition of its muscular tissue must be equal to these demands. Affections such as degenerations, atrophies, and dilatations may consequently, on the whole, prohibit its employment.

Whether the action of digitalis is of use in those ailments where the insufficient filling of the arteries is not dependent on abnormalities of the heart, but upon other causes, cannot be decided, on account of the deficiency of rational observations. As regards this, there may at any moment be an indication in pneumonia for the better filling of the arteries, if the nature of the pulse points to a deficiency of blood in them; the object is then to favour the circulation in the lungs, and to exercise a beneficial influence upon the inflammatory process.

Up till now digitalis has only been employed in this affection for the purpose of checking the fever and the great frequency of the pulse. A diminution of temperature only takes place under the influence of this remedy, because either the cause of the fever, *i.e.*, pneumonic exudation, is removed, or the metabolism and the evolution of heat lessened under its influence upon the circulation. The latter occurs, however, only in the more advanced stages of the action of digitalis; if the paralysis of the heart has already begun, the effect is to be compared to a collapse which comes on in the course of a severe illness, in consequence of paralytic conditions of the heart, of the respiration, or of other areas. One can cause an artificial collapse, and thereby lower the temperature of the body. Quite aside from the question as to whether such a treatment of the fever does any good, the fact remains that it is at all events fraught with danger to the patient.

The administration of the members of the digitalin group in inflammation of the lungs should only be for the purpose of inducing a better filling of the arteries where this seems indicated, and consequently perhaps for the purpose of effecting the encouragement of the pulmonic circulation. As regards this, good results can be imagined possible in those cases where habitual congestion of the lung leads to hæmorrhages, and to the occurrence of tuberculosis. It is, moreover, not improbable that in such conditions a better filling of the arteries, kept up for a long time, may exercise a favourable influence upon the nutrition in general. In past times digitalis played an important part in the treatment of well pronounced phthisis of the lungs.

The pure active principles have till now been scarcely employed in medical practice. Digitalis is generally used, and in certain cases squills.

The former contains, in addition to the three substances belonging to this group, certain active decomposition products of them, namely, digitaliresin and toxiresin, which act after the manner of picrotoxin, and by stimulating the corresponding areas of the medulla oblongata, cause slowing of the pulse, contraction of the vessels, and, in the more advanced stages of their action, convulsions. It is, however, improbable that these substances come into consideration during the administration of digitalis; still less can any effect be expected from digitonin, which likewise is contained in fox-glove, and which is chemically and pharmacologically closely related to saponin.

When digitalis is made use of in medical practice, only the action of digitalin comes into question. In squills no active constituents other than scillaïn have as yet been discovered.

The question whether any of the above-named pure substances are adapted to therapeutic purposes cannot at present be answered with certainty. Some are either hard to obtain in the requisite quantity without inordinate cost, or else cannot be got at all, while others are not applicable because of their peculiarities. To the latter belongs digitoxin, which is absolutely insoluble in water, and consequently is slowly and irregularly absorbed. A dose of 1 mg. ($\frac{1}{60}$ grain) was quite inactive, while 2 mg. ($\frac{1}{30}$ grain) caused in the same person violent poisoning, which lasted no less than four days. Moreover, the substances which are soluble in water do not enter readily into the blood and tissues, and apparently are slowly excreted; consequently, after prolonged use of digitalis, at times an accumulation of the active substances in the blood takes place, and this brings about unexpectedly and undesiredly strong so-called cumulative actions. The substances to be employed must consequently be such as are absorbed and excreted as uniformly as possible. These claims are probably best fulfilled by an alkaloid named erythrophlœin, which is contained in the bark of *Erythrophlœum guineense* (sassy bark). Yet, along with the digitalin action, it causes also the picrotoxin-like action of digitaliresin (Harnack and Zabrocki). Whether the latter action is objectionable must be settled by trying it upon patients.

Of the above-mentioned substances those which deserve special attention are the chemically pure digitalin, adonidin, scillaïn, oleandrin, and apocynin. These are, it is true, almost insoluble in water, but yet sufficiently soluble to render absorption from the stomach possible. Helleboreïn, which is easily soluble in water, must also be mentioned.

The subcutaneous application of these substances is hardly to be thought of, because even those which are soluble in water cause phlegmonous inflammation more or less readily,—*e.g.*, digitoxin does this in dogs, after doses of $\frac{1}{10}$ to $\frac{1}{2}$ mg. ($\frac{1}{600}$ - $\frac{1}{120}$ grain). Closely connected with this is their action upon the stomach and intestine, which sometimes causes gastric disturbances, diarrhœa and other symptoms of gastro-intestinal catarrh, to come on during the use of digitalis.

These effects may likewise act as a hindrance to the employment of a substance otherwise suitable. That squills act so strongly upon the intestinal canal is perhaps dependent upon the fact that in it many colloid substances occur, more particularly the carbohydrate sinistrin, which substance favours the passage of scillaïn into the intestine, but may retard its absorption.

To judge from preliminary investigations, there may be here included a resinous substance found in *Grindelia robusta*, and *G. squarrosa.* It is insoluble in water, but is soluble in alcohol, ether, and carbonate of soda. In large doses it seems to act like digitalin (Dixson).

THE VERATRINE GROUP.

Veratrine, which is contained with other alkaloids in various species of veratrum, paralyses, almost without exception, every part of the peripheral and central nervous systems. The paralysis is preceded in various organs by stimulation. The voluntary muscles are at first put into a peculiar state, in which they contract in a normal manner after being stimulated, but only come back to their former length very slowly. Consequently in frogs the extension of the limbs takes place quickly, as under ordinary circumstances, but the drawing together of the outstretched limbs takes place very slowly (v. Bezold). This process is associated with an increased formation of heat at each contraction, therefore with increased metabolism (Böhm and Fick).

The appearances shown by the hearts of these animals exhibit a similar character. The systole goes on as usual, but the passage into the diastolic state demands a relatively long time (Böhm). The long continuance in the more or less contracted state gives the heart, in many cases, the appearance of having been poisoned with digitalis.

As the action advances the muscles become paralysed: especially readily does this occur in the case of the muscle, and probably also of the motor ganglia, of the mammalian heart.

No one has as yet investigated the origin of the symptoms on the part of the glands and digestive canal, which consist in the formation of a frothy secretion upon the skin in the case of frogs, and in salivation, nausea, vomiting, colic, and copious stools in the case of mammals, and which come on without any sign of inflammation.

Veratrine acts at first as an irritant or stimulant, and then as a paralysing agent upon the terminations of the motor nerves of the voluntary muscles, upon those of the inhibitory fibres of the heart, upon those of the sensory nerves of the skin and mucous membranes, and, finally, upon those of the centripetal nerve fibres in the lung.

Among these effects, the irritation of the sensory nerves of the skin, tongue, throat, stomach, and conjunctiva deserves special notice. If applied to the mucous membrane of the nose, the alkaloid causes sneezing; and if to the eyes, it evokes tears; placed upon the tongue a burning sensation results, in the throat and stomach a feeling of rawness and a prickly sensation. When it is diffused through a fatty mass, or dissolved in an alcoholic liquid, and then applied to the skin, there follows at first a feeling of heat and tingling, which may increase to a burning and stinging pain, without redness or any sign of inflammatory irritation being visible; after this there comes on local numbness, with a feeling of coldness and fluffiness. The employment of veratrine in the form of an ointment as a local anæsthetic in neuralgia, especially of the face and supra-orbital region, is based upon this action. Some certainty of success is only to be expected when the seat of the neuralgic affection is quite superficial, as is mostly the case in supra-orbital neuralgias.

Of the actions upon the central nervous system, all of which accompany general paralysis and end in it, tetanic spasms are more evident in the case of frogs, and paralysis of the respiratory centre in the case of mammals. These, in conjunction with the powerful depression of the heart's action, even in the milder degrees, bring about in man symptoms which correspond to those collectively designated with the name of "collapse."

The occurrence of the latter is more particularly favoured by the fact that, like the emetics proper—apomorphine, emetine, and tartar emetic—veratrine causes very severe nausea, with its accompanying symptoms, which, in little children and weak people, may be sufficient of itself to bring about collapse.

Consequently veratrine can be looked upon as a means of inducing a state of artificial collapse. Giddiness, dimness of the sight, a feeling of general weakness and feebleness, at first acceleration, then retardation, as well as weakness and irregularity of the pulse, nausea, retching, and other gastro-intestinal symptoms, spasmodic hiccup lasting occasionally several days (Wachsmuth), coldness and paleness of the skin and face, are the symptoms which have been seen to occur in the healthy and in the sick after repeated and even single doses, averaging 3 mg. ($\frac{1}{20}$ grain) of acetate of veratrine.

It is, moreover, easily seen that the disturbance of so very many functions also brings about a very considerable lowering of the temperature of the body, probably in consequence of the diminution of metabolism. This can also be effected in patients who have a high fever-temperature.

Consequently veratrine has often been recommended and employed as an antipyretic remedy, especially in pneumonia and acute articular rheumatism, which diseases do not of themselves so readily cause collapse as, for instance, typhoid does. Yet we dare not forget, in using it thus, that it is more a question of causing artificial collapse in such a case, than of reducing the fever (Wachsmuth). A discussion of the question whether, and to what degree, such a collapse may help in the treatment of the morbid processes which tend to cause exhaustion through too great a consumption of the constituents of the body, lies far beyond the realm of pharmacology.

It is possible that the action of veratrine upon the muscles might be made use of with advantage therapeutically, were it possible to evoke it to a decided degree without any risk.

THE ACONITINE GROUP.

This group embraces the various and as yet but very insufficiently investigated alkaloids of the various *species* of aconitum and delphinium.

Among these are specially to be enumerated—1*st*. Crystallisable aconitine, $C_{33}H_{49}NO_{12}$ in *Aconitum napellus*; 2*d*. Pseudaconitine or nephaline, $C_{36}H_{49}NO_{12} + H_2O$ crystalline, in the root *Aconitum ferox*; 3*d*. Japaconitine, $C_{66}H_{88}N_2O_{21}$ crystalline, in the root of *Aconitum japonicum*; 4*th*. Delphinine, $C_{22}H_{35}NO_6$ crystalline; 5*th*. Staphisagrine, $C_{22}H_{33}NO_5$, amorphous.

The actions of these alkaloids exhibit essentially the same fundamental character, and affect the heart and central nervous system. In frogs these organic tracts become at once paralysed; in mammals the destruction of the irritability of the respiratory centre predominates.

The earlier investigations were carried out mostly with the so-called German aconitine of commerce, which seems to be a mixture of an amorphous aconitine not yet well investigated, and of various other alkaloids and their decomposition products. The above alkaloids were experimented with more especially by Böhm and his pupils, Molênes (with the aconitine of Duquesnel), Langaard (japaconitine), and v. Anrep. Comparative pharmacological investigations carried out with chemically analysed preparations are still wanted.

With like quantities japaconitine acts most strongly (Langaard), next to it comes crystallised aconitine, which upon one occasion caused the death of a man after a dose of 3 to 4 mg. ($\frac{1}{20}-\frac{1}{15}$ grain). Then follow pseudaconitine and delphinine, and, finally, the amorphous commercial preparations, which are relatively weak.

The essence of the action of the alkaloids upon the heart consists in the motor ganglia of the heart being at first stimulated and then paralysed. In the case of crystallised aconitine the stimulation has, however, been denied (v. Anrep).

In frogs the cardiac pulsations become accelerated, then retarded; thereupon, just as after digitalis, they become irregular, and finally leave off in diastole, which is due to paralysis of the motor ganglia, and which at first can be removed in a characteristic way by stimulating the vagus, just as has been observed after poisoning with amorphous aconitine (Böhm). The heart at last loses its irritability entirely.

In mammals, too, the paralysis of the heart is always demonstrable, although less distinctly, as are also the actions upon the central nervous system. After small doses of these poisons, and in the incipient stages of their action, changes in the frequency of the pulse and blood-pressure are dependent upon various causes which to a certain degree are inexplicable.

German aconitine, even after section of the vagus and after poisoning by atropine, causes slowing of the pulse without reduction of blood-pressure, while acceleration of the pulse precedes paralysis of the heart. *Pseudaconitine* causes at first slowing of the pulse and sudden sinking of blood-pressure. These are results of a central stimulation of the vagus, and are absent after the section of it, or after the administration of atropine. The dyspnœa also ceases after this more or less entirely, and therefore probably depends upon the above-mentioned disturbances in the circulation. *Delphinine* causes in small doses rise of blood-pressure and increase in the frequency of the pulse. These effects remain even after section of the cervical region of the cord, and are consequently referable to stimulation of the cardiac ganglia.

The course of the poisoning in mammals is controlled by the *paralysis of the respiration centre* and its results. As regards this, the above-mentioned alkaloids are almost identical with each other. This is true also as regards the *vaso-motor centres.* These are particularly affected by delphinine, and are first of all rendered insensible to stimuli which reach them centripetally.

The disappearance of the vascular tonus occurs before the decrease of cardiac activity, consequently it is customary for large pulse waves to accompany the sinking of the blood-pressure.

In consequence of the rapid cessation of the respiration, *the direct paralysis of the remaining parts of the central nervous system* has rarely time to become very pronounced. Delphinine is specially distinguished by the very early extinction of the reflex irritability in mammals as well as frogs.

The *convulsions* which occur in mammals do not probably depend upon suffocation alone, for they are weakest after *staphisagrine,* or even totally absent, although in the case of poisoning with this alkaloid death is entirely due to suffocation.

In *frogs* general convulsions have been seen after delphinine in a few cases only (Böhm and Serck): on the other hand, more or less *fibrillar twitchings of the muscles* are never absent. In the case of these animals, the cause is to be found in an irritation of the motor nerve terminations, which ultimately become paralysed, so that a curarine-like action results.

Of the actions upon the remaining peripheral areas the *irritation of the terminations of the sensory nerves* in the skin and mucous membranes must be specially noticed. It very much resembles that due to veratrine, seeing that blunting of the sensibility follows the original state of irritation.

Moreover, these alkaloids cause salivation, and also an increase of other secretions. How far they influence the inhibitory apparatus of the heart after the manner of atropine cannot in the meantime be decided. An action upon the *muscles* cannot with certainty be proved.

The rather numerous *empirical indications* for the application of the aconite given in past times have for the present been entirely given up in Germany. A *rational basis* for the use of these alkaloids, excepting for neuralgias, cannot in the meantime be deduced from their actions. Aconite, therefore, which was introduced in the course of last century by Storck, can now be considered without hesitation as an obsolete remedy.

THE COCAÏNE GROUP.

Cocaïne is an alkaloid contained in the leaves of the *Erythroxylon coca.* Like veratrine, it acts upon the terminations of the *sensory nerves;* but, unlike it, it does not cause any stimulation, but induces numbness from the first. Hence, at the places where it is applied, especially on the mucous membranes of the eye, ear, nose, mouth, urethra, and vagina, a *superficial anæsthesia* is produced, while the sensory fibres proper remain intact. The sensitiveness to pain, however, is not removed in cases of deep wounds, on account of its purely superficial action; the sensitiveness to reflex action is toned down, and for this reason all superficial *operations* can be *executed* if cocaïne has been applied beforehand, without the usual painful sensations being felt by the patient.

When given in *considerable* doses, it acts also upon the *central nervous system.* In *mankind* it *accelerates* the *pulse* and *respiration,* and induces giddiness, discomfort in the head, dilatation of the pupil, and hallucinations. In animals, death results apparently because of paralysis of respiration.

In human beings, after doses of 0·1–0·39 g. (1½–5 grains), uncomfortable sensations of all sorts are removed. This action probably depends upon the numbing of the sensitiveness of the ends of the sensory nerves, through which many different kinds of uncomfortable and disturbing reflexes are toned down.

THE COLCHICINE GROUP.

Colchicine is a nitrogenous but not very clearly basic body, contained in all parts of the colchicum plant. Its isomeric and crystalline decomposition product, *colchiceïn*, which is acid in reaction, is also pharmacologically active. Detailed investigations into the action of perfectly pure colchicine are as yet wanting. However, we know the symptoms caused in man and animals by the preparations found in commerce, which are probably contaminated with the presence of colchiceïn (Schroff, Albers, Harnack, Rossbach, Roy).

In frogs it causes the disappearance of muscular irritability (Harnack), spasms, and paralysis of the central nervous system. On *mammals* it evokes, in addition to the latter, violent *symptoms* in the *stomach and intestine*, after the manner of emetine (Schroff, Roy), consisting in vomiting, diarrhœa, great redness, swelling, and ecchymosis of the intestinal mucous membrane. Upon the heart the poison does not seem to exert any special influence. The blood-pressure sinks gradually in consequence of lowering of the irritability of the vasomotor centres, this contributing to the symptoms of paralysis on the part of the central nervous system. Consequently, even after large doses, stimulation of the splanchnic is sufficient to cause a rise in blood-pressure (Rossbach). In cases of general poisoning, paralysis of the peripheral terminations of the sensory nerves is said to take place, while solutions of colchicine, applied to the surface of the skin, do not affect its sensitiveness in any way (Rossbach).

It is not possible to deduce from the above actions any rational indications for the employment of the preparations of colchicine. At present no great reliance is placed upon the empirical use of it in rheumatic and gouty conditions, and in cases of excessive formation of uric acid.

THE QUININE GROUP.

Quinine is a universal poison to all kinds of organic elements in the animal body, and not only for those to which, as to the muscles and nerves, specific functions are ascribed, but also to those protoplasmic areas in which merely the processes of nutrition and metabolism are carried on. Aside from moderate inflammation of the tissue at the point of application, and from a slight increase in the reflex irritability of the spinal cord in frogs, and from an irritation, as yet doubtful, of the muscular fibres of the abdominal organs, this alkaloid causes in all cases paralysis from the very outset, which always increases with the dose, and ultimately ends in the destruction of the functions of the organs attacked by it, even when the latter have to carry on merely chemical processes.

The *organism as a whole* in the various races of animals succumbs through the result of the destruction of those functions which are most important for its continuance. In warm-blooded animals death is caused through the cessation of the respiration and of the heart's action. In the case of frogs it is due mainly to the latter cause. As regards the lowest organism, we can only notice the cessation of all signs of movement. The latter are suppressed at once in *Infusoria* of every kind, if the fluid in which they are present contains 0·5 to 1·0 per mille of quinine (Binz). Under like conditions the colourless blood corpuscles cease their amœboid movement. In frogs diapedesis in inflammation of the mesentery is restrained, either in consequence of this paralysing action on the part of quinine (Binz), or in consequence of the disturbances of the circulation, which come on under its influence (Zahn, Köhler). Infusoria and other entozoa which are to be found in the blood of those animals are, on the other hand, neither paralysed nor killed in cases of quinine poisoning.

Quinine acts much less energetically upon *bacteria*, and upon *putrefactive and fermentative organisms* in general, than upon the above-mentioned structures. Their movements only become suppressed, and their further development prevented—the processes of fermentation and putrefaction correspondingly hindered or arrested —when the quantity of quinine in the fluids or solids reaches from 2 to 8 per mille.

Of those tissues which consist of contractile protoplasm, only the *cardiac muscle* in mammals will have more or less lost its irritability by the time death occurs, although the *voluntary muscles* are, even in the case of frogs, but little altered. The paralysis of the heart at first brings about slowing of the pulse, and at last, in the case of frogs, ends with this organ coming to a stand-still in the relaxed state, and with the utter annihilation of its irritability.

In man and mammals small doses of the alkaloid cause at first *increased frequency of the pulse*, and hand in hand with this comes *an increase of blood-pressure.*

The cause of these appearances has not been sufficiently explained. It is supposed to be due to a lessening of the tonus of the cardio-inhibitory fibres of the vagus, either in consequence of the lessened irritability of their central origins (Schlockow), or of their peripheral end organs (Block, Jerusalimsky). Paralysis of those parts only takes place after large doses (Jerusalimsky), but it is not always under these conditions demonstrable (Schlockow, Lewitzky), or at any rate it is not total (Binz). The rise of blood-pressure may also be dependent upon a direct affection of the cardiac muscle (Lewitzky), through which an increase in the volume of the pulse is brought about, just as after digitaline, probably in consequence of an increase in the extensibility of the muscular substance (Chirone).

Large doses of quinine, in man 1 g. (15 grs.) and upwards, cause from the outset *reduction in the frequency of the pulse and fall of blood-pressure.* These are due to commencing paralysis of the heart; this, along with paralysis of the respiratory centre, brings about a fatal result.

It has almost unanimously been observed by numerous investigators that in man, and animals also, *diminution of the spleen* takes place under the influence of quinine. It is not possible as yet to determine decidedly whether this is due to a direct stimulation of the involuntary muscular fibres. The spleen, even after it is dilated, in consequence of the section of the nerve plexus passing to it, contracts under the influence of quinine (Mosler, Jerusalimsky). Analogous contraction in the uterus, and the correspondingly increased peristalsis of the intestine, have been considered by some as dependent upon stimulation of the involuntary muscle fibres (Chirone, Monteverdi.)

The action of quinine upon the *nervous system* influences only the cerebro-spinal portions of the latter, while in the peripheral areas no special changes can be discovered, except the somewhat doubtful paralysis of the terminations of the inhibitory fibres of the vagus, and the atropine-like action upon salivary nerves, when the alkaloid is directly injected into the gland (Heidenhain).

The cerebral symptoms in man consist in giddiness, headache, singing in the ears, difficulty in hearing, and even deafness, sensitiveness to light, darkening of the field of vision and double vision, confusion of ideas, drowsiness, and stupor.

Probably there is as little ground for considering direct irritation of definite areas of the brain as the cause of these symptoms, which have been designated as "*quinism*," as in the milder cases of alcoholic intoxication, and morphine narcosis. Yet this cannot be maintained with the same certainty as in the case of the latter poison. In frogs quinine causes a narcosis resembling that of morphine.

Loss of consciousness, delirium, coma, and at times convulsions, form *the final stage of the action of quinine in man.* When recovery occurs there at times remain behind permanent disturbances of the sensory functions, especially deafness, but also amblyopia and even blindness. Death is due in man to collapse. In animals, after subcutaneous injection of amorphous quinine, it results chiefly from paralysis of the respiration, which precedes the stoppage of the heart (Heubach).

The actions of quinine upon the *spinal cord and medulla* are more or less marked in mammals by the rapid approach of changes in the activity of the respiration and heart. Through small doses of amorphous quinine the reflex irritability of the spinal cord and vascular nerve centres is not lowered in the case of rabbits (Heubach), but in these animals after 0·04 g. to 0·12 g. per kg. ($\frac{1}{3}$ – 1 gr. per lb.), in dogs after doses of 0·16 to 0·18 gr. per kg. (1$\frac{1}{4}$ – 1$\frac{1}{2}$ grs. per lb.), along with the access of a very low blood-pressure the irritability of these centres is destroyed as well for the reflex as for the direct stimulation during artificial suffocation (Schroff).

It is impossible in the meantime to decide with certainty what is the origin of the frequent though irregular *convulsions* after large doses. In frogs there is always present an increase of the reflex irritability after doses of 1 – 5 mg. ($\frac{1}{60}$ – $\frac{1}{12}$ grain) of amorphous quinine; paralytic symptoms on the part of the brain occur independently of the cardiac action, the reflex irritability alone continues a long time (Schlockow).

It is easy to understand that in consequence of the energetic action of quinine upon the respiration and the heart, that *temperature and also metabolism are lowered* in a manner resembling that of the veratrine group (p. 78), because of the preliminary stages of collapse. Although after veratrine the last-mentioned results may take place in the way indicated, it may be taken for granted in the case of quinine, upon the very ground of its therapeutic actions, that it exerts an influence upon the tissues at the *seat of metabolism* which is quite independent of the alterations in the respiration and heart. The experimental proofs of this view are not at present numerous, but yet there are some; and to these belong first of all the observation that quinine prevents the formation of acid in the blood, both before and after coagulation (Binz), and that it to a great extent retards the formation of hippuric acid in the kidney. It consequently is probable that the alkaloid reduces within definite limits the *decompositions, oxidations, and synthetic processes* which are going on in the tissues of the living body, and so proportionally lessens metabolism and the formation of heat.

Many attempts have been made to determine the *behaviour of the metabolism and the body temperature* under the influence of quinine. The investigations in this direction have afforded results at one time indefinite and variable, at another mutually contradictory. This depends, on the one hand, upon the actions of quinine itself, and, on the other, upon the methods employed and the conditions of the experiment. After small doses a *rise* of the temperature of the body has been met with (Waldorf; Duméril, Demarquay, and Lecointe; Bonwetsch), after larger doses usually a *reduction.* The quantity of carbonic acid was found in experiments on cats with the *Pettenkofer* respiration apparatus sometimes a little lessened, sometimes a little increased (Bauer and v. Boeck). In tracheotomised rabbits which breathed through *Müller's* valves no difference could be observed between the poisoned and unpoisoned animal as regards the excretion of carbonic acid and absorption of oxygen during the space of a quarter of an hour (Strassburger).

Similar oscillations are shown in the results as to the *nitrogenous constituents of the urine.* Generally a reduction of urea has been observed. Some experimenters were unable to find any influence of quinine upon the excretion of the latter (Unruh). In fowls the production of uric acid was diminished after internal administration of quinine; after subcutaneous injection it was found increased (Jansen).

From all these results the only certain decision that can be reached is that in the healthy body, and under all conditions, a constant influence upon the temperature and metabolism of the body cannot be maintained by the use of quinine. The variations of temperature after small doses of quinine seem to be dependent on the mutual co-operation or opposition of the action of the various factors. The alkaloid generally causes inflammatory *disturbances at the seat of application*, especially in the case of the mucous membranes, but they are only of moderate intensity. Consequently, after its use, slight catarrhal conditions of the stomach result, and these bring about disturbances of digestion, so that the food taken is not used up, and as a consequence a reduction of metabolism becomes perceptible. In this manner is to be explained the lessening of the formation of uric acid in fowls after its internal administration. If the rise in the pulse, blood-pressure, and temperature, so often observed after small doses, be associated with increased appearance of the products of metabolism, this disturbance of digestion may more or less counteract the effect. But it is very difficult to get a general view of all the circumstances which come into play.

Larger doses pretty constantly lessen temperature and metabolism both in normal conditions and in fever. What share, on the one hand, the direct influence of the alkaloid upon the tissues, and, on the other, a certain amount of artificial collapse has in this action, is very hard in a general way to decide. If in acute diseases with continuous fever we find a decided and rapidly occurring fall of temperature after the use of the remedy, we may say the premonitory symptoms of an action akin to collapse are rarely absent, this action is to be judged of in the same way as that of veratrine.

After the long use of small doses, such as are given, for example, in hectic fever, the direct influence upon the metabolic processes becomes much more distinctly possible, yet the affection of the stomach in these cases is very difficult to avoid.

We are still quite in the dark as to the nature of the *action of quinine in intermittent fever*, and in malarial diseases in general, since it is not here a question of reducing the temperature, but of preventing the periodical rise of it. To begin with, we have not that knowledge which is so necessary for the explanation of the above curative action. Very striking are the statements that in patients afflicted with ague, after the suppression of an attack of fever by means of quinine, the excretion of nitrogen by the urine (Sidney Ringer, Senator) and evolution of heat (Naunyn and Hattwich) are increased exactly at the time the attack was due, in spite of the fact that the temperature of the body remains normal.

It would be presumptuous to attempt to decide in the treatment of intermittent fever which of the actions of quinine really comes into play—whether it is that which affects the seats of metabolism or that which affects the circulatory and nervous system, or whether in fact it is due to that combination of these two actions which is a special characteristic of the base as compared with the rest of the chinoline series.

The employment of quinine in malarial diseases, and in other conditions which have a typical course, such as, more particularly, neuralgia, has consequently at present only a *purely empirical basis.* The rules according to which in such cases it is to be employed belong to the realm of special therapeutics, and do not need to be repeated here.

Just as in former times the attempt was made to replace quinine by more palatable vegetable substances, so quite recently the attempt has been made to employ an artificial compound of the aromatic series in its stead.

There can be no doubt as to the ultimate success of the attempt to find among the innumerable aromatic compounds some which will be able to retard the metabolic processes in a very striking manner, and even better than quinine, without causing any action upon the heart and respiration worthy of mention, or even upon other muscular and nervous organs. The first step in this direction has been made by means of *salicylic acid.* Along with this, chemical and medical industry has already collected a considerable number of aromatic substances, some containing nitrogen, some *not.* This number will probably soon increase very considerably. It would hardly aid the cure of the sick if every one of the substances recommended were to be accepted straight away, and if ailing mankind were compelled to act as a test for the advantageous employment of the products of chemical industry.

Even though it were on the whole easy to discover febrifuge remedies, we cannot, on the other hand, in the slightest foresee whether a substitute for quinine will ever be found for the treatment of intermittent fever, and the ailments which belong to this category. Even the other quinine alkaloids, with the exception of cinchonine, which is contained in chinoidine, are not to be compared with it.

CHAPTER II.

SUBSTANCES WHICH THROUGH THEIR MOLECULAR PROPERTIES CAUSE ALTERATIONS OF VARIOUS KINDS AT THE POINT OF APPLICATION.

ALTHOUGH in the case of nerve and muscle poisons the actions occur only after absorption from the blood, as we are wont to say, numerous substances cause molecular alterations similar to those of the above poisons, but only in those parts of the body with which they come first of all into direct contact; therefore, on the outer skin and on the mucous membranes of the respiratory, digestive, and urinary organs, as well as on the conjunctivæ, absorption of these substances is certainly not excluded; but, in consequence of the alterations which they undergo before or after being taken into the blood, they become inactive, or experience during their diffusion through the organism so great a division and dilution, that in the individual organs they are present at any given time only in quantities so small as to exert no effect. Nevertheless concentration may take place in the excretory organs again, and in them similar alterations may be brought about to those at the point of application. For those reasons, cantharidine, which is unchanged in the organism, causes not only exudative inflammation on the skin, but causes also corresponding changes in the kidneys, if it come to be absorbed in considerable quantities.

The actions of this class of pharmacological agents consist in *a spurring on of various functions*, or *stimulation of the nutrition* of tissues in general. The former concerns more particularly the sensory nerves, the organs of taste and smell, and the motor mechanism in the intestinal canal, and through the latter all tissues at the point of application are more or less concerned, and every degree of functional irritation and inflammatory disturbance of nutrition is brought about.

In the case of mixtures of various substances which do not act upon each other, a mutually *opposite "molecular" action* may none the less show itself, so that the properties of one or other of the constituents, and consequently their behaviour upon absorption and their influence upon the tissues are modified more or less through the presence of the remaining substances. In this sense there are substances which, corresponding to the old-fashioned idea, are called "corrective" in action. To this group belong first of all the excipients which in various ways play a great part in the mouth, stomach, and intestinal canal, and consequently can be placed at the head of this class of remedies.

A proper *pharmacological classification* of this class is not practicable here, because, as a rule, we do not deal with chemically pure compounds, but with drugs and their raw products, in which often variously acting constituents are contained. In many cases we do not know the latter at all, and are consequently unable to refer them to any definite group. We must, therefore, meanwhile content ourselves with placing their therapeutic use in the foreground, and with classifying them accordingly, although terpenes, which are represented by oil of turpentine and the mustard oil, as well as the certain class of aperients, are also pharmacologically well defined.

EXCIPIENTS.

Gum, sugar, mucilage, and other pharmacologically indifferent substances, are used for making pills, granules, lozenges, powders, capsules, wafers, and similar medicinal forms, for the purpose of mechanically enveloping the active materials. But, apart from these, vegetable substances which are soluble in water, or which are colloid, and which swell up in it, such as gum, mucilage, starch, paste, dextrine, and the like, have another quite special value as excipients. They are able *to lessen the sharp but especially sour taste of many substances*, as if to cover it over, although they themselves are quite tasteless. With the same quantity a liquid such as lemon water may taste far less acid when it contains these colloids than when it does not do so, as may easily be seen by making a simple experiment with a solution of gum or starch and tartaric acid.

The colloid substances found in *vegetables and fruits*, and called *pectins*, play a very important part in this respect. The acid taste of fruit depends not only upon the amount of acid and of sugar present respectively, but essentially also upon the proportion of the former, compared with the quantity of gum and pectins. In the raspberry there is less sugar than in the currant to the unit of acid, yet it contains thirteen times as much of the colloid substance as the latter (Fresenius), which consequently is acid, while the former is a sweet fruit.

Similar conditions are to be met in the case of *beer*, but the latter under otherwise similar conditions—that is, when the amount of alcohol and hops are the same—is less watery and less bitter when it contains an extra amount of colloid extracts.

Whether the peculiar masking action of colloid substances extends down *into the stomach and intestine*, and so exerts such an influence that the action of irritants and pungent agents upon the mucous membrane is weakened, cannot for the present be decided, although it is not improbable. We may still, however, believe with sufficient certainty that all indigestible colloid substances, especially gum and vegetable mucus, not only remain themselves a long time in the intestinal canal, but *also are able to retard the absorption of other substances*. In consequence of this, food, when it is kept too long in the stomach and intestine, undergoes fermentation and abnormal decomposition, and so gives rise to disturbances of the health: the difficulty of digesting many vegetables and fruits, the harmfulness of artificial ones, the so-called heavy character of thick beers, are for the most part to be referred to such conditions as these.

One can advantageously employ the influence exerted by gum and other colloids upon the absorption of other substances, in the *construction of those medicinal prescriptions*, the active constituents of which are intended to pass into the intestine, but which are usually absorbed in the stomach. To these belong more particularly the tannins, which we consequently in catarrh of the intestine prefer to give with mucous decoctions, or in the form of crude vegetable extracts.

Moreover, too, the *preference of extracts*, as compared with the pure active constituents contained in them, in the treatment of *intestinal affections*—of those of opium instead of morphine, of extract of belladonna and nux vomica instead of atropine and strychnine respectively—may be explained by the colloid portions of those extracts favouring the passage of the medicinal substance into the intestine.

Among the drugs used for the above purposes are—salep, containing starch and vegetable mucus; gum arabic, containing arabic acid; tragacanth, containing bassorin; mallow, and marsh mallow flowers, tussilago leaves, &c., containing only vegetable mucus.

Various lichens were in past times considered specially adapted for cases of illness. This belief still survives here and there, especially among the laity; but the jellies which are made from them can now-a-days only be considered as having the importance of excipients. The chief of these substances are carrageen and Iceland moss, the former containing a peculiar mucilage, and the latter a carbohydrate lichenin, very like starch.

Liquorice contains a peculiarly sweet, amorphous glucoside, which swells up in water, and is called glycyrrhizic acid. This latter has a mild aperient action, but from the way in which the preparations of liquorice are usually employed, they have almost only the same value as any other colloid substances.

SPECIFIC OLFACTORY AND GUSTATORY REMEDIES.

(a.) *Articles of Luxury and Correctives of Taste.*

Vegetable substances *which have a pleasant taste and smell are used, on the one hand, for improving these properties in the case of substances obnoxious in this respect* (correctives of taste), and, on the other hand, they are employed for making refreshing beverages and other pleasant drinks. A specific medicinal action on the part of the individual constituents hardly comes into question; it is purely a matter of the pleasure which the sick and the healthy derive from them. Beverages form a very suitable and agreeable means by which cold water is introduced into the system in great quantities. Were they introduced in the form of clysters instead of by the mouth, they would have no value beyond that of any inert watery fluid.

Not only *sweet and acid*, but also *aromatic and bitter substances*, may be used in all sorts of combinations for the fabrication of pleasant beverages for the sick. It is no thankless task on the part of the physician when he pays special attention to this aspect of treatment. A judiciously chosen beverage is often found to afford greater benefit than many a highly valued prescription.

To this category of therapeutic agents belong marrows, sugars, syrups, spices, ethereal oils (especially of the varieties of citrus), organic acids, extracts of meat, wine, and the articles of luxury which contain caffeine, in the use of which the specific actions of their constituents is not always in question.

(b.) *Teas.*

These form a special group of substances which improve taste. It frequently happens *that large quantities of warm water must be brought into the body*, *e.g.*, in order to assist in bringing about perspiration, or of effecting relaxation in spasmodic states. Since, however, warm water easily excites nausea, or even vomiting, it is usual to add the pleasant aromatic flowers, fruits, and herbs, which are called tea. By this means the infusion becomes changed into a pleasant beverage. The small doses of ethereal oils which are contained in these drugs can hardly be considered as exerting any specific action.

Numerous vegetable products can be used for the purpose of making such tea-infusions—*e.g.*, elder flowers, linden flowers, sage leaves, chamomile flowers. As regards the sage leaves, the presence of tannin in them helps their action, for they are chiefly used in astringent gargles. In the case of the chamomile, the essential oil is of importance, because of its direct action upon the stomach.

(c.) *Olfactory Remedies.*

A considerable number of volatile substances are employed as olfactory remedies, not only to act as pleasant perfumes, but also to exercise *reflex influences* passing from the nasal membrane to the central nervous system, and especially the medulla oblongata. Sneezing, we know, owes its origin to a process of this nature.

At every *irritation of the nasal mucous membrane*, especially when caused by various gases and mixtures of gases, a reflex process in the track of the trigeminus comes into action, which always shows itself in the breathing by an expiratory spasm coinciding with the simultaneous closure of the glottis, and further, in the circulation, by slowing of the heart, due to the central irritation of the inhibitory fibres, and finally by a concurrent rise in the arterial blood-pressure (Hering and Kratschmer). The prolongation and stoppage of the heart's contraction has been observed at the beginning of the inhalation of chloroform (Dogiel, Holmgreen), or when other irritant substances act upon the nasal mucous membrane (Krishaber, Marey, François-Franck). Upon such a reflex irritation of the medulla oblongata depends the use of olfactory remedies *in faintings*, asphyxia, and other conditions.

It is not the specifically odoriferous substances which one chooses for this purpose, but those *volatile compounds* which either coincidently or exclusively excite a considerable degree of sensory irritation. Volatile fatty acids, especially formic and acetic acids, ammonia, oil of mustard, when highly diluted, and various kinds of ethers, are the substances best adapted for this purpose. Among the popular remedies employed are the empyreumatic products formed by burning feathers, or a smouldering candle. Amongst the products in the latter case is the irritant and ill-smelling acroleïn.

(d.) *Ill-smelling Substances as Neurotics.*

Many of the vegetable substances possessed of a bad smell are extensively employed *when there is a general increase of sensory and motor sensitiveness* of the nervous system, especially in hysterical conditions. Those chiefly made use of are *asafœtida* and *valerian root.* Since in these no peculiar active principles can be discovered, we are compelled to believe that the almost unquestionable curative results are connected with the smell which is so disagreeable to persons with strong nerves, and that this occurs essentially and in a reflex manner. The peculiar influence of the smell of valerian upon the psychical behaviour of cats rather favours the view as to a specific reflex influence.

The fluid called borneol present in *oil of valerian* readily becomes oxidised to common camphor, and seems to act in large doses like the latter. Possibly it might be of use under similar circumstances.

The constituents of asafœtida proved quite inert in cases where experimenters tried it upon themselves (Buchheim and Semmer).

THE AROMATIC AND BITTER STOMACHICS.

From the earliest ages it has been customary to ascribe to a large number of aromatics and bitter substances in the vegetable kingdom a beneficial influence upon the functions of the stomach and intestine. Since the designation aromatic and bitter, which refers only to taste, at the same time serves to characterise the therapeutic importance of these substances, the phrase also shows that as yet little is known of their action upon the stomach. As a matter of fact, all that can with certainty be said is, that by means of these remedies slight catarrhal affections of the mucous membrane of the stomach, and also certain functional disturbances, such as dyspepsia, which imply no very serious anatomical changes, are occasionally removed, and troublesome sensations in the digestive organs are frequently dispelled. Consequently such remedies are pleasant to most sick persons belonging to this category, who, as a rule, repose great trust in them.

Certain substances, such as those commonly used as *spices*, cause a general *stimulation of the gastric mucous membrane.* It is, to begin with, not improbable that by them the hyperæmia occurring during digestion may be increased, and the formation of the digestive juices favoured. Nevertheless, in *experiments on digestion* in dogs, where portions of albumen were introduced into the stomach through gastric fistulæ, sewn in thin pouches, some being without, others in contact with the drugs in question, the results showed that salicin, resin of absinthe, quinine, pepper, mustard, salt, and other substances do not favour the digestion of albumen, but always to a slight degree impede it (Buchheim and Engel, Schrenck). In this there may have been an *antifermentative action* by means of which the solution of the albumen was impeded, just as has been shown in the case of some of these substances in regard to alcoholic fermentation (Buchheim and Engel). No importance can be attached to the minute acceleration of the solution of fibrins under the influence of small doses of quinine found by L. Wolfberg in his experiments upon digestion.

On the other hand, it seems not improbable that these substances also act antiseptically, and in cases of illness occasionally prevent *abnormal decomposition and fermentation*, without hindering the digestion of albumen.

If this possibility be allowed, and the probability be considered that a slight stimulation of the mucous membrane of the stomach is perhaps not able to hurry the normal process of digestion when it is at its best, but is able either to strengthen or stimulate and set it going again so soon as it is beginning to succumb to the consequences of slight disorders, and through over stimulation of the mucous membrane of the stomach, due to a surfeit of eating and drinking, then in this action of aromatics and spices there is a sufficient explanation of the curative effects which are at times observed after their use in the treatment of the above-mentioned condition of the stomach. It may also be conceived, but it cannot be quite certain, that the *movements of the latter* are increased when a general moderate stimulus is applied to this mucous membrane, and a favourable influence is thereby exerted upon the digestion. Those drugs which contain large quantities of ethereal oils are given for the purpose of stimulating the *movements of the intestine*, and so removing collections of gas present in states of colic.

It is very difficult *to review upon rational principles the numerous drugs and their preparations* which are still to be found in the pharmacopœia, and which can be classed under the heading of stomachics. Many are quite antiquated, and others are quite superfluous, because the same object can be attained by a great number of these remedies, while a few would be quite sufficient to meet all necessities. In the construction of the pharmacopœia, the further reduction of this long list of herbs, blossoms, fruits, and roots, which as a rule no one but the apothecary ever sees, has evidently only been avoided for the reason, on the one hand, that the idea of the possibility of finding some specific effect has not been given up, and, on the other, that the old-fashioned tinctures are considered as particularly good, and contain a large number of these drugs.

(a.) *Spices and Aromatic Stomachics.*

The drugs which are derived from the *various species of citrus* contain aromatic and bitter substances, such as *limonine* and *aurantiïne*, as well as the ethereal oils belonging to the terpenes. These oils are of importance for flavouring purposes, and consequently must be regarded as of some use.

Unripe bitter oranges contain an abundance of a bitter substance, and hence may be ranked with the bitter stomachics.

Cinnamon contains an ethereal oil, which consists essentially of the characteristically smelling and hot tasting *cinnamic aldehyde.* Its preparations are chiefly important as flavouring agents.

The oil of cloves, which occurs in cloves, consists of *eugenol* and of terpenes, and acts as a powerful irritant wherever applied.

Nutmegs are very decidedly poisonous: the active constituent seems to decompose easily, at the same time forming an ethereal oil. The oil of nutmeg is composed of a mixture of substances which belong to the class of terpenes and camphors. Oil of mace has a similar composition.

Other spices which we may mention here are *cardamoms*, *ginger*, *turmeric*, *galanga*, *acorus*, *imperatoria*, *and pimpinella*.

All of *these culinary and medicinal spices*, of which the first-mentioned are members of the order Zingiberaceæ, contain ethereal oils, and also hot or pungent aromatic constituents, which are in most cases but little known.

The fruits of the umbelliferous plants *coriander*, *carraway*, *fennel*, *anise*, *waterfennel* and *dill*, contain oils chiefly belonging to the terpenes, but no pungently tasting ones, such as occur in the roots of the umbelliferous *imperatoria*, *angelica*, *pimpinella*, *&c.* The above fruits are very much employed as so-called *carminatives* for the removal of gases from the intestine.

(b.) *Bitter Stomachics.*

Various *alkaloid* and other substances, particularly strychnine and quinine, are distinguished among the special muscle and nerve poisons by their intensely bitter taste; hence they are reckoned, when employed in small doses, as also belonging to the *bitters*. But one may set up a pharmacological group of bitter substances, which is characterised by the members which belong to it not causing, at any rate in the higher animals, any striking effects, either upon the nerves or the muscles. Hence, evidently their bitter taste is the only pharmacological test for them. One may indeed accept it as true that these substances exert a special influence upon certain nervous elements which are in the wall of the stomach, and which are concerned with the process of nutrition, an influence similar to that which they exert upon the nerves of taste. Nevertheless, at present there is not a single genuine proof to justify such a belief. After the *injection of calumbine and cetrarine into the blood*, rise of arterial pressure was observed to follow a preliminary but transient lowering of it (Köhler). Still it is doubtful whether this action is characteristic of the group of bitters. It seems much more probable that each substance acts in its own way in this respect.

The pure bitters are distinguished from the spices by their causing *no general stimulation of the mucous membrane of the stomach*, but, on the other hand, they have, like the spices, a certain amount of *antiseptic action*.

From a practical point of view, these bitter substances are also interesting, because they are used in the fabrication of *bitter brandies*, which are both beverages and popular stomachics.

The chief drugs which we may mention here are quassia, absinthe, menyanthes, gentian, centaury, hops, benedict, dandelion, calumba, coto, serpentaria, cascarilla, canella, cusparia.

It may be incidentally mentioned here that in the use of the so-called spring cures, in which the juices of fresh herbs, especially dandelion, are used, the mild aperient and diuretic effect is partly due to the organic salts present.

As regards calumba, the starch, and probably other colloid bodies present, facilitate the passage of its active principles into the intestine, and hence its effect in cases of diarrhœa. The absence of tannic acid makes it difficult to speak with certainty as regards the nature of the action. Perhaps it is a case in which, like that of cotoine and paracotoine, the circulation and nutrition of the intestine is improved through dilatation of the vessels.

No one of these bitters has any special advantage as compared with the rest. Some physicians will prefer one, and others will prefer another. In the case of some of them, the presence of tannic acid comes into consideration.

Closely connected with the above are a number of other plants containing bitter principles. Among these we must mention the *Achillea millefolium*, which contains the very bitter achilleïne, and the musk milfoil (*Achillea moschata*), which grows upon the Alps, and in which the bitter resinous ivaïn occurs along with an ethereal oil.

DRUGS AND PREPARATIONS USED FOR ALL SORTS OF PURPOSES, BUT NOW MOSTLY ANTIQUATED AND OBSOLETE.

It is quite impossible to distinguish the use of substances in this group. Among them are anti-cachectics, correctives, and adjuvants so-called from their relation to the action of other remedies; then come tonics, nervines, diapnoics, stomachics, digestives, diuretics, and many others, amongst which are the "cure-all" of cajeput and arnica. As a matter of fact, they have merely the weak action of ethereal oils, belonging mainly to the groups of the terpenes and camphors. It need scarcely be stated that even by these remedies, *e.g.*, arnica, many a therapeutic result may be attained, especially by their use in covering a bad taste, or as a stimulant to the stomach, skin, &c., but even for this purpose they can very well be dispensed with. Pharmacology is at present just as *powerless* as is therapeutics to make anything out of these substances.

The ethereal oils of the Labiatæ, such as *thyme*, *melissa*, *serpyllus*, *rosemary* and *lavender*, belong chemically, and probably pharmacologically, to the groups of the terpenes and camphors; indeed common *camphor* is contained in the oils of lavender and rosemary.

Ethereal oils, including terpenes and camphors, and other constituents, are contained in such drugs as the following:—arnica, cajeput, laurel, myrrh, orrice root, melilot, feringrea, elecampane.

Such drugs as sassafras wood, guaiac wood, or orrice root, the violet plant, condurango bark, and borage, have been used chiefly for the preparation of the antiquated decoctions which were employed as *blood purifiers*, *sudorifics*, and *diuretics* in particular, and antidyskrasics, resolvents, and alterants in general. Quite recently *condurango bark* has been added to the list *as a remedy for cancer.*

The presence of tannic acid in it probably explains the certain degree of efficacy it shows in *gastric* affections.

Scurvy Grass is employed in the disease so named, because it is found that sailors smitten with this disease recover as soon as they reach any country in northern latitudes where this plant forms perhaps the only vegetable or salad to be found.

DISINFECTANTS AND STIMULANTS FOR THE URINARY ORGANS.

It is a distinctive character of a number of vegetable substances, especially of those belonging to the terpenes, that after their absorption from the stomach they pass through the kidneys, mostly in an unaltered condition, and in doing so exert a therapeutic effect in various ways. While, on the one hand, preparations of juniper are employed to increase the urinary secretions, copaiva and cubebs are made use of for the purpose of exercising a beneficial influence, more especially upon the urethral mucous membrane when the latter is affected with gonorrhœa.

In the juniper berries there are organic salts of the alkalies which can increase the urinary secretion in the same way as other salts of this kind. Further, the constituents of the ethereal oils, when they reach the kidneys unaltered, cause irritation of the latter. This in more pronounced forms leads to inflammation, but in its milder forms only to increase of the permeability of the renal tissue for the constituents of the urine, especially the water.

The ethereal oils in the above-named drugs consist for the most part of terpenes, which are rapidly absorbed because of their volatility, and form in the body conjugate glycuronic acids. These pass into the urine in the form of very soluble salts. Whether in doing this they, like other salts, accelerate the excretion of the water, has not yet been investigated. No great importance is to be ascribed to them in this direction. On the other hand, the conjugate compounds of the terpenes play, at least in certain cases, an important part in the urine, for they render the latter aseptic immediately before its excretion. This has as yet only been observed to occur after the administration of balsam of copaiva, but may also be true of other substances, especially cubebs.

The urine of man and animals, after taking balsam of copaiva, does not as a rule decompose so readily as under ordinary circumstances. It remains for a long time perfectly clear, and even when triple phosphates are ultimately precipitated, and the surface is covered with mould, putrefactive bacteria are totally absent, or, if present, are only in small numbers.

To this character of the urine is due the importance of balsam of copaiva, and probably also of cubebs, in the treatment of the urethral mucous membrane when affected with gonorrhœa.

If only a few drops of ordinary urine remain suspended on such a mucous membrane, they may under these conditions rapidly decompose, and so retard the cure. If the urine, on the other hand, only decomposes less readily, it becomes relatively harmless, and so one hindrance to the cure is removed. Disinfectants brought directly into the urethra cannot be so successful, because under these circumstances they are swept away by the frequent passage of the urine.

Of the various constituents of balsam of copaiva, it is more particularly the terpenes which appear in the urine in the form of conjugate glycuronic acids. They appear partly also as ethereal sulphuric acids. The terpenes, even ordinary oil of turpentine, yield conjugate compounds with glycuronic acid, and are consequently suitable for rendering the urine more or less aseptic. The only condition requisite in practice is that the necessary quantities of the substances in question be brought into the stomach for a sufficient length of time without injuring the functions of the latter. Whether balsam of copaiva and cubebs really answer these claims best, and whether their preference in practice is justifiable, or whether, again, other substances injure the stomach less, and render the urine more aseptic, must be settled by systematic investigation. In early times, in addition to these remedies, not only the juniper berries and various balsamic resins, but even turpentine oil, were used and lauded.

THE CUTANEOUS STIMULANTS.

Stimulation of the skin plays an important part in therapeutics. A great number of substances pertaining to all sorts of pharmacological groups are employed for this purpose. They are applied over every extent of areas of the skin, even over the whole surface of the body, for the purpose of evoking either the milder forms of *sensory stimulation*, and the preliminary stages of *rubefaction*, or of causing the most intense forms of irritation of all the tissues of the skin *with exudative inflammation.* The object aimed at in these results is either to alter the skin or affected part, and the morbid production upon it, or to exert an influence indirectly upon more distant organs.

Mild degrees of inflammatory irritation, especially if kept up for a considerable time, may cause the disappearance of *exudative hypertrophies*, and of other pathological products at and around the point of application, as, for example, opacities of the cornea.

It is not a matter of any specific nutritive or functional action, such as has been believed to be the case with iodine, but more or less exclusively a question of the intensity and extent, as well as the duration and uniformity, of the irritation. How deep the influence of the latter extends after prolonged use cannot be determined, either in general or special cases. Zuelzer painted one side of a rabbit for a fortnight with cantharides collodium, and found anæmia of the parts situated more deeply. Yet the result can hardly assist one in deciding the question.

An explanation of the effects exerted upon distant organs by means of *blisters* and *issues* can hardly be thought of, because there is perhaps not a single case in which the results expected, and at times observed, can be traced with absolute certainty to the use of the remedy. There would be a risk of wishing to explain what perhaps never existed.

The stronger irritants, which, when applied for a short time, cause acute *pain and intense redness of the skin*, certainly at times exert a beneficial effect upon various morbid, especially inflammatory, rheumatic, and neuralgic conditions. This effect is due to an action upon organs more or less distant from the place stimulated, and is brought about reflexly through the stimulation of the sensory nerves.

Formerly the cure used to be considered dependent on direct *abstraction* of blood from the affected organ. We now know that sensory stimuli exert reflexly the greatest influence upon the conditions and functions of numerous organs. Certain it is, that we must, from the therapeutic point of view, grant that such influences play a great *rôle.* What is the connection between them and the cure in the individual case, or even in general, and what routes the reflex actions take, and which of the possible alterations is the one which really constitutes the prime factor in the cure,—all these points are beyond our power to decide. We must simply be content with registering the reflex influences which are induced through the skin.

Very much in the same way as sleep may be interrupted by sensations, so consciousness and other functions of the brain, when in abeyance during *faints and somnolent states*, can be roused again to activity by strong cutaneous stimuli.

Especially powerful is the action of the latter upon the *organs of respiration and circulation.* Yet the explanation of the symptoms observed in man and animals is rendered difficult, because there is almost no way of excluding the influence exerted by the psychical processes upon the functions of these organs, an influence almost always present under these circumstances. Moreover, there has been a want of methodical and accurate investigation into the general influence of counter-irritation upon the various areas. The accounts at our disposal refer to individual sensory areas. In general, the number of the *respirations* increases with mild sensory stimuli, and falls considerably with strong ones (P. Bert, Langendorff). To this is probably due the stoppage of the respiration in man, when a large area of skin is brought into contact with cold water. That it is a question here of the reflex contraction of the bronchial muscles, as was once believed, is not indeed impossible, but does not seem so probable.

The *blood-vessels* become reflexly contracted or dilated through sensory stimuli (Lovén, Naumann). The various vascular areas behave differently in this respect, yet no further details can be given with certainty. As a rule, a moderate degree of stimulus causes a *contraction of the vessels*, and, as a result, the arterial pressure rises. Usually, too, the frequency of the heart's beats increases, as in other cases is wont to be the case with a rise of blood-pressure not exceeding certain limits, if increased resistance be opposing the exit of the blood from the left ventricle (v. Bezold and Stezinsky).

Dilatation very soon follows, then contraction, especially when the stimulus is a strong sensory one. This dilatation also is accompanied by a more or less pronounced retardation of the cardiac pulsations, due to a reflex stimulation of the vagus, conveyed in the case of the frog along the sympathetic. But when in mammals the heart-beats become very frequent, the blood-pressure sinks (Marey and François-Franck).

In consequence of these alterations in the circulatory organs, *the distribution of the blood* must certainly suffer considerable oscillations in the different organs, and this we must consider as the curative factor in the treatment of affections of the internal organs by counter-irritants. These are mostly employed in hyperæmia and congestion, inflammation of the lungs, the digestive canal, the brain, the spinal cord, and membranes of the two latter. In these cases, the utmost one can expect is an alteration of the distribution of the blood, even though it be but transient.

Finally, it has been noticed that sensory stimuli exert an influence upon the *temperature and metabolism of the body.* Upon stimulation of the central portion of a sensory nerve, the rise of arterial blood-pressure is accompanied by a simultaneous fall of the internal temperature of the body (Heidenhain). Strong stimuli of any kind applied to the skin probably act in the same way through an increased loss of heat, due to the dilatation of the peripheral vessels. They cause a fall of the temperature of the body, while the slighter degrees of dilatation cause the latter to rise (Röhrig and Zuntz), probably in the main because of increased production of heat. At least an increase in the consumption of oxygen and excretion of carbonic acid has been observed in rabbits to which mustard poultices had been applied (Paalzow).

The *rules and more definite indications and contra-indications for the employment of cutaneous stimulation* in cases of disease, rest upon a purely empirical foundation, and pertain to the practice of medicine. However, reference must once more be made to the fact that in *no* case, not even that of iodine, is it a question of a specific action, and that it in no way depends upon the nature of the remedy, but upon the strength and duration of its influence upon definite and more or less extensive areas of the skin. To estimate these conditions rightly in each individual case is the duty of the physician.

From the properties and pharmacological behaviour of the individual substances can be deduced *which of the numerous remedies* available for such purpose *is to be chosen* upon each occasion, in order to achieve with certainty the form of irritation desired.

If it be desired to produce a moderate stimulation of the whole surface of the body, or at any rate, of large tracts of it, by means of *baths*, *lotions*, and *embrocations*, dilute solutions of acids, of alkalies, and of salts, or else alcoholic fluids, ethereal oils, and volatile substances, are chosen for the purpose in general.

When a limited area of the skin is to be subjected to rubefaction, and at the same time to receive a strong *sensory stimulation*, preference is given to one or other of the preparations of oil of mustard. *Cantharidin*, in the form of cantharides plaster, acts excellently for bringing about exudative inflammation with the formation of *blisters*.

To these therapeutic categories correspond three pharmacological groups, and these are—firstly, the *turpentine oil group*, amongst which all terpenes and many hydrocarbons and ethereal oils can be reckoned; secondly, *the mustard oil group*; and finally, the *cantharidin group*, inclusive of the so-called acrid substances.

All bodies which are *volatilised* with *moderate ease* at ordinary temperatures, cause, without exception, a more or less decided general irritation at the point of application. This is to be considered as due to the fact that these, being volatile substances, rapidly penetrate into the tissues, that they here diffuse with great ease, and that, being in a state of molecular division, they act upon the elementary tissues as foreign bodies, so to speak. The various oils of turpentine, many ethereal oils from the vegetable kingdom, numerous substances belonging to the fatty series, *e.g.*, chloroform, chloride of ethyl, petroleum, also benzol, and other compounds of the aromatic series, cause local irritation essentially in this way. Hence also the volatile acids of the fatty series, *e.g.*, acetic acid, and among the alkalies ammonia, are more irritant than the non-volatile compounds of these groups.

When chemically indifferent *volatile substances have, in addition, specifically irritant properties*, as is so notably the case with *ethereal oil of mustard*, the action is unusually violent. They then cause, in a very short time, every stage of a general irritation, from redness of the skin to exudative inflammation with formation of blisters, terminating in suppuration and destruction of tissue.

We might employ oil of mustard as a universal cutaneous irritant, were it possible to regulate its penetration sufficiently. But this is unattainable in the stronger degrees, because the altered tissue is nowhere sharply demarcated from the healthy. If we blister the skin by means of mustard applications in the same way as by cantharides plaster, not only does the outer layer of skin, which yields the exudation, pass into a state of inflammation, but the subjacent parts are attacked to a considerable depth, and readily suppurate; consequently the healing of blisters caused by mustard oils only takes place slowly.

When, on the other hand, *specifically irritant* substances, which are *not volatile* at ordinary temperature, *e.g.*, *cantharidin*, are applied to the skin in a vehicle which dissolves the cutaneous fat, *e.g.*, in a fatty ointment or resinous plaster, they penetrate the epidermis but slowly, and come to the cutis, where they at first excite only an exudative inflammation, leading to the formation of blisters, while the deeper layers remain still fairly intact. The consequence is, that in this case healing results quickly and easily, without suppuration or destruction of tissue.

(a.) *The Turpentine Oil Group.*

To this belong the various *terpenes of the coniferæ*, the so-called turpentine oils; further, also those terpenes which have been already mentioned in connection with various drugs. All turpentine oils are almost equally irritant; *savin oil* alone is distinguished for a specially strong inflammatory action. When it gets into the stomach it rapidly causes gastro-enteritis, and the appearance of blood in the urine.

Of the preparations cited below, and which can be suitably employed for one purpose or another, a few individual ones are quite sufficient for all cases.

Turpentine oil, when kept for a long time in bottles partially filled with air, *contains ozone*, and can oxidise phosphorus to hypophosphoric acid. It has consequently been recommended for oxidising phosphorus in the stomach in cases of poisoning. If it be used in these cases, we must take care that it contains plenty of ozone, otherwise it can only aid the absorption of the phosphorus by dissolving it.

The turpentine oils got from firs and pines (wood-wool oil), as well as from the mountain pine (*Oleum pini pumilionis*), differ pharmacologically from common oil of turpentine, only by their smell not being so pungent as that of the latter.

Liniment, with ammonia, also opodeldoc, spirit of camphor, and other similar liniments and spirituous fluids, contain volatile substances—ammonia, camphor—whose irritant actions upon the tissues at the point of application only come subordinately into consideration in the construction of the pharmacological group. These preparations are mentioned here in consideration of their being used as cutaneous stimulants.

(b.) *The Mustard Oil Group.*

The ethereal *oil* of black mustard, which is isosulpho-cyanate of allyl, is formed in powdered mustard-seed in the presence of water by the action of a ferment myrosin upon myronate of potassium ($C_{10}H_{18}KNS^2O^{10}$); the latter thereby decomposes into one molecule of oil of mustard ($CNS.C_3H_5$), sugar and acid sulphate of potassium. In the freshly prepared *mustard poultice* and the freshly moistened *mustard leaf* there is very little oil of mustard present. It is only after some little time that the quantity of the latter attains its maximum. During the application the activity of the preparation increases, and this is a circumstance which is to be remembered in measuring the strength of the action, according to the time that the mustard blister is in contact with the skin.

Oil of mustard is also made synthetically. The isosulpho-cyanic ethers of other alcohol radicals designated in chemistry as mustard oils have not till now been pharmacologically investigated, nor in any way practically made use of. Butyl mustard oil has been mentioned under the head of scurvy grass.

(c.) *The Cantharidin and Euphorbin Group.*

The active constituents of the cutaneous irritants which belong to this group are not volatile at ordinary temperatures. *Cantharidin*, from Spanish flies, and *euphorbin* from euphorbium resin, are only anhydrous acids. The former is active, both as an acid and in the form of salts, and separates from the latter unaltered upon the addition of acids. Euphorbin is inactive after its transformation into euphorbic acid, and after its separation from its source no longer passes back into the anhydride form.

Cayenne pepper contains the chemically indifferent crystallised capsaïcin $C_9H_{14}O_2$, which is the intensely pungent and irritant constituent, and perhaps also the oily looking *capsicol.*

Cantharidin, euphorbin, capsaïcin are soluble in alcohol, ether, liquid hydrocarbons, and fatty oils.

In this group we may reckon *mezereïn* of mezereum, bark got from daphne mezereum, *anemonin*, which occurs in various ranunculaceæ, and the oil-like *cardol*, $C_{21}H_{30}O_2$, which is contained in the fruit of *Anacardium occidentale* and *A. orientale*, and in the poison sumach.

APERIENTS.

The aperients which come from the vegetable kingdom correspond to the cutaneous irritants in the nature of their action. Just as the latter evoke an irritation or stimulation of the skin, so do the former in the intestinal canal, and this leads *to increased peristaltic movement*, and consequently to a rapid evacuation of the intestinal contents. The latter remain more fluid, because they get no time for consolidation.

The irritation may affect all the elements of the intestinal wall, if the substance employed belong, like *gamboge and croton oil*, to the *universal irritants*. The mildest degree of its action is sufficient to induce increased peristalsis and evacuation. After large doses inflammation of the intestinal canal (gastro-enteritis) rapidly results.

Some aperients, however, *affect other parts so little* as to cause no noticeable irritation on the skin, for example; but yet in the intestinal canal they not only cause an increase of the peristalsis, but even induce inflammation. This is especially true of *colocynth.*

Many substances, to which belong *jalap*, *resin*, and the active principle of *castor oil*, only meet with the conditions necessary to their efficiency after they get into the bowel, because they are soluble in the intestinal fluids *only*.

In certain individuals it seems to be essentially a *case of irritation of the motor ganglia of the intestine*, upon which the movements of the latter are dependent. In this category must be reckoned *rhubarb, buckthorn bark, senna, and podophyllotoxin* (present in commercial podophyllin). Hence it is possible to cause diarrhœa by injection of an infusion of senna into the blood, or of podophyllotoxin hypodermically.

Any irritant which does not cause general poisoning after its passage into the blood could be employed as an aperient, were it possible to apply it under all circumstances locally to the intestinal canal. But all volatile substances, as well as all those that are soluble in water and crystalloid and quickly absorbed, pass even from the stomach into the blood and fluids of the tissues, and in consequence of this may not even pass into the intestinal canal at all. This can only occur with facility when the substance is either insoluble in the contents of the stomach, or has a colloid structure, and accordingly is with difficulty absorbed.

Castor oil, *croton oil*, *gamboge*, and *jalap* resin are insoluble in watery fluids, and consequently pass the stomach unchanged. In the intestine they are dissolved by the alkalies of the bile and pancreatic juice, or, like castor oil, in fact digested. The resin of gamboge consists essentially of gambogic acid. This in the pure state is less effective than the same quantity of resin (Christison), because the gum which is found in these drugs not only helps emulsification (Buchheim), but, being a colloid, also favours the passage into the intestine of the gambogic acid, which is sparingly soluble in water.

The active constituent of senna is the non-nitrogenous *cathartic acid* (Stockman). It is soluble in water, but upon boiling splits up into sugar and anthracene derivatives closely allied with chrysarobin. It is a colloid, both in its free state and in the form of its salts, and consequently is not absorbed in the stomach. Rhubarb and buckthorn bark either contain this acid or compounds closely related to it.

The *crystallisable soluble colocynthin*, when pure, does not under all conditions cause diarrhœa; hence, apparently, it also seems to need the presence of colloidal substances, such as occur in colocynth, for it to be with certainty carried into the intestine.

Crystallised aloïne is almost inert, but there forms from it by decomposition an amorphous modification, which is found, already formed, in *Aloe lucida*, and which seems to cause its activity. In the case of the latter, the bile plays a part as yet unexplained. At any rate, aloes acts, when given in clysters, exactly in the same way as any lukewarm fluid; but after the addition of ox gall, a violent irritation and inflammation of the rectum results (Buchheim, Sokolowski, and v. Cube).

Of the two active constituents of podophyllin, *podophyllotoxin* is but sparingly soluble, and *picro-podophyllin* not soluble at all in water, The former acts, when given subcutaneously, as a poison to the central nervous system also (Podwysotzki).

The action of the members of this class can for the present only be ascribed to an increase of the peristaltic movements, especially of the colon. The movements of the small intestine are also, under normal conditions, so energetic that its contents get into the large intestine whilst still fluid. Diarrhœa only occurs when the consolidation in the latter organ is prevented by acceleration of evacuation.

The increase of the quantity of fluid through augmentation of the intestinal secretion seems, from the outset, not improbable, but has not been as yet proved. In any case genuine transudations into the intestine are only seen when, through these substances, or through experimenting on the exposed intestine, inflammation of the latter is caused.

Every increased peristalsis of the intestine goes hand in hand with *hyperæmia*, which in the more intense form may advance as far as to cause extravasation of blood into and upon the mucous membrane. In such cases, especially, however, when the aperients directly cause an inflammatory irritation (croton oil and gamboge), and act preferably upon the lower part of the intestine, the hyperæmia extends to the neighbouring pelvic organs. Thus in *the gravid uterus contractions* may be caused, ending in abortion and premature labour. The more acrid purgatives must consequently be handled cautiously during pregnancy. Even in *feverish conditions* it is better to avoid them, because any irritation may increase the fever.

None of the aperients is adapted to *subcutaneous application.* Some strengthen the peristalsis only when locally applied; the others are not known in the pure condition. Whether podophyllotoxin is suitable for this purpose it is impossible at present to settle. Perhaps the peculiar active principles of senna, rhubarb, and buckthorn, when they have been obtained quite pure, will show themselves as particularly suitable to this form of application.

The *well-defined pharmacological classification* of the individual aperients is for the present impossible, because the active principles of many have not yet been discovered. This is especially the case with croton and castor oils. In the latter the action is not dependent upon the ricinoleic acid, nor apparently upon the irritant substance present in the seeds. This substance is insoluble in ether and alcohol, but soluble in water, and whether given by mouth or hypodermically, causes violent gastro-enteritis, leading to death. Boiled in water, it rapidly decomposes, becoming inactive; but castor oil so heated retains its activity even for a long time (Dixson).

Senna leaves lose their nauseously tasting constituents in alcohol, without sacrificing their aperient properties. Hence the value of spirituous extracts. It is possible that the active constituent of rhubarb is identical with that of senna. This is, perhaps, also the case with *Fructus rhamni cathartici* (buckthorn berries), and possibly, too, with *Cortex frangulæ* (buckthorn bark). This latter bark is prone to cause colic, for which the great amount of tannin present in it is probably to blame.

SULPHUR AS AN APERIENT.

As regards its action in the intestinal canal, sulphur belongs to the pharmacological *group of the alkaline sulphides.* Yet it can be classed with those aperients which cause evacuation by increasing the peristalsis of the intestine.

If pure, finely divided sulphur gets into the *stomach*, it remains there quite unaltered. If it reach the intestine, it meets there with alkaline contents, and *part* of it *gets converted* into *sulphide of sodium* (Buchheim and Krause). This acts very caustically on all of the tissues, and in consequence of this causes increased peristalsis of the intestine and evacuations. Since, however, the quantity of alkali carbonates in the intestine is limited, and the transformation of the sulphur into the sulphide results very slowly, this substance does not as a rule act very energetically. The stools are rarely fluid, but merely become pultaceous.

Finely divided sulphur can consequently be employed with advantage as an aperient in those cases in which a rapid and perfect evacuation of the intestinal contents is not wanted, but where it is merely desired that the *fæcal masses should get past the rectum, and especially the anus, in a less consistent state, and therefore with greater ease.* It is upon this ground that the employment of sulphur, in past times, in *hæmorrhoidal* complaints is still applicable; in this latter condition, it is necessary as far as possible to avoid irritation due to hard fæcal masses, the evacuation of which, moreover, is usually very painful.

Other aperients which generally cause fluid stools are in these cases unsuitable, because they easily affect the nutrition of the patient when long used. Moreover, it is difficult, if not impossible, to graduate the dose so as to cause merely pultaceous stools, for often the action either fails, or diarrhœa comes on.

Since the transformation of the sulphur in the intestinal canal is limited by the quantity of alkali, *the strength of its action is to a certain degree independent of the dose made use of*, and remains uniform even after the usual maximum dose is overstepped. Consequently, when it is so, diarrhœa can almost certainly be avoided, without one having to fear that the desired result will fail. Only when the diffusion of the sulphur is very great, as in *milk of sulphur*, and large quantities enter at once into the intestine, does the formation of the sulphide of the alkali result with relative suddenness; the latter is not quickly enough absorbed or decomposed by the formation of sulphuretted hydrogen, and as a consequence violent intestinal symptoms result. Accordingly the less finely divided *flowers of sulphur* do not act so powerfully as the milk of sulphur when given in like doses. The former must consequently be preferred to the latter for practical purposes.

That there is in the intestine, as a matter of fact, an alkali compound, and that it is formed with the sulphur, and that the aperiency is due to this, follows certainly from the fact that the quantity of sulphuric acid in the urine gets increased (Griffith, Buchheim and Krause), which otherwise would be unexplainable, and further, that when sulphur and carbonate of soda are taken simultaneously, more sulphuric acid appears in the urine than when each is taken into the stomach alone, or diffused in oil (Buchheim and Krause).

ANTHELMINTICS.

The medicines employed for the extirpation of parasites, and which should properly speaking be reckoned among the disinfectants, must possess similar properties to the aperients as regards their passage from the stomach into the intestine, *i.e.*, they must be *but slowly absorbed.*

After arriving in the intestine, they should not, like the aperients, cause increased peristaltic actions, but through their molecular properties so act upon the tape-worms, round-worms, and other similar parasites, that the latter are either killed, or at least rendered very sick, and then driven into the lower part of the intestine, whence they are readily removed by aperients. The remedies are not individually effective *against every kind of parasite.* The extract of *bracken root*, in which *filicic acid* (and especially an amorphous modification of it) is the active agent, is used preferably for *Bothriocephalus*, while for the *Tænia solium* the *pomegranate* bark and also *kamala* are recommended. *Kousso* flowers are recommended for both forms of tape-worm. *Worm seeds*, in which the active principle is *santonin*, are unanimously considered a sovereign remedy for *round-worms*, which pass away dead after the administration of this substance alone, without its being combined with aperients.

Certain rules must be conformed to in the *removal of tapeworms* if the treatment is to succeed.

It is important to choose the time when the segments of the *Tænia* are being passed with the fæces, further to lessen the quantity of the intestinal contents by a suitable diet, and then to administer the anthelmintic, and finally to give an aperient of suitable strength, and at the right time, so that copious stools may come on rapidly, without the latter assuming a fluid and watery consistency. The execution of these rules demands some practice, hence the explanation of the successfulness which certain tape-worm doctors sometimes attain to in this field.

All the drugs belonging to this group, and their active constituents, when given in large doses, cause *poisonous symptoms*, affecting portions of the central nervous system.

Santonin acts in a peculiar way upon the *brain*, and has given rise to poisoning in children. Among the cerebral symptoms *yellow* and *violet* vision are especially striking. The former results readily from medicinal doses.

After 0·5 to 2·0 g. (8 to 30 grs.) santonin in adults, 0·1 to 0·7 g. (= 1½ – 10 grs.) in children, the following symptoms have been observed, amongst which the convulsions are the most constant; flashes of light before the eyes, hallucinations of smell and taste (E. Rose), headache, lassitude, prostration, uncomfortable sensations in the region of the stomach, nausea, vomiting, with trembling of the limbs, convulsive twitchings and movements in the muscles of the face, eyes, and jaw, which are at first intermittent and unilateral and afterwards general, and a trembling voice (Binz), Convulsive attacks and cessation of the respiration, tetanic conditions and convulsions, with stoppage of the respiration, characterise santonin poisoning, both in mammals and frogs.

After the use of *pomegranate bark* severe *intestinal and cerebral symptoms* have been seen to occur; the former often consist in vomiting, pains in the abdomen, and diarrhœa, probably dependent upon the large amount of tannic acid in the drug. With these symptoms are associated headache, giddiness, stupor, spasmodic trembling of the limbs, and even well pronounced convulsions.

These symptoms depend upon various alkaloids obtained by Tanret from the bark of the pomegranate root, more particularly *pelletierin*. This latter is also the active body in the treatment of tape-worms, and is best administered in the form of the tannate, which of all the preparations passes most readily into the intestine.

Kousso flowers, of which the active constituent is *Koussin*, and *kamala*, when given in large doses, cause diarrhœa without any important symptoms, so that we can omit the use of aperients, especially when employing kamala.

CHAPTER III.

THE ACTION OF WATER AND OF SALINE SOLUTIONS.

THE chemical relations of water and of a number of salts of the alkalies and the alkaline earths to one another, and to the tissue forming substances of the organism, are intimately connected with the conditions necessary to life; even small deviations in the absolute and relative quantity of these constituents can bring about marked changes in the behaviour of the organic functions and of metabolism.

These changes one can easily cause artificially by the administration of water and salt in extra amount, and in many cases they can be taken advantage of for therapeutic purposes.

1. WATER.

When brought into the body in large quantities, water causes actions which are connected with the *solubility and the distensibility of the tissues.*

Watery solutions may be considered as *molecular combinations* of water with the substances in solution, and they differ from their compounds in many particulars. They can dissolve many constituents of the body in greater amount than pure water, while their ability to cause the expansion of substances which are capable of imbibing water is usually less. Their power of passing through membranes is different from that of water, both as regards filtration and endosmosis. Water as such never comes into contact with the living tissue, but becomes transformed into a solution while it is still in the stomach; at all events it only enters the blood in this form.

Water causes a *local abstraction of the salts, and a swelling up of the tissues.* If one bring isolated living organic elements into contact with pure water they die off rapidly, because of the abstraction of the salts and other soluble substances which are absolutely necessary to the continuance of the life of such structures. In order that the integrity of the latter may remain, the solution permeating them must have a definite concentration and composition. Alterations in this respect cause disturbances in the function and nutrition of the tissues.

The slighter degrees of this action of water come into consideration in "*water cures*," in which pure thermal or other water is taken in large quantities for a long time. In this *rinsing* out of the stomach the superficial layers of epithelium necessary swell up considerably, and are soaked through and through. They thus are rendered incapable of living, and cast off. The process gives rise to more *active regeneration*, by which the pathologically altered tissues are replaced by normal ones, and morbid conditions of the mucous membrane are improved or even cured.

In baths the action of water hardly, if indeed ever, comes into question, because water can neither penetrate the epidermis, nor directly alter it to any material extent.

Only in *protracted bathing* do the superficial layers of the skin swell up. This alteration occurs more readily in morbid portions of the skin, especially where the epidermis has been removed, as in wounds and sores. In such cases the effect is similar to that on the stomach. Slight desquamation of the altered tissue results, and the wounded part is, moreover, protected from infection.

In general, water in the form of baths is merely a *solvent agent* for medicines, especially for neutral and alkaline salts, or, as in the application of the so-called "indifferently" cold and warm springs, the bearer of a higher or lower temperature, and in this form a purely *physical agent*, which exercises those balneologically important effects upon the temperature of the body and metabolism, as well as upon respiration and circulation.

Water passes very rapidly from the digestive canal into the blood and other fluids of the body. The *cause of the absorption* is not sufficiently understood. *Endosmosis* can hardly be at work here, because the process is only one-sided, for no endosmotic stream goes out of the blood into the intestine. Were it otherwise, the solidification of the fæces would be unexplainable.

Moreover, the absorption of the water cannot be referred to *filtration*, because we cannot believe that while the tissues are so yielding, the difference of pressure which is necessary to filtration exists between the intestinal tube and the organs or the blood.

It seems just as little probable that water finds its exit out of the digestive tract by means of *open stomata*. Were this the case, all fluids would be rapidly absorbed, while the solution of Glauber's salt, as a matter of fact, behaves as regards this quite differently from the solution of common salt.

On the contrary, the absorption of the water may be considered as a *process of imbibition* which takes place with special readiness on the mucous membrane, in the serous cavities, and in the subcutaneous cellular tissues; the portions of organs which are thus capable of swelling up, and which come first of all into contact with water, take it up, and give it off again in the form of serous lymph, or it gets extracted from them by the more concentrated blood as it streams past.

The excretion of the water by the kidneys may be reasonably considered as essentially a filtration which is dependent upon the blood-pressure in the vessels of the glomeruli. Whether in these processes, as in the passage of solid substances into the urine, a specific activity of the epithelium of the renal tubules comes also into play, is not quite certain.

Perspiration only takes place after the administration of a large quantity of water, and when the skin is at the same time in a state of congestion; this latter is practically brought about by warming the surface of the body, either by preventing it cooling, or by raising the temperature around. In this, the nerves which control the perspiration probably develop increased activity.

That portion of the water which is necessary to the maintenance of the normal state of distention of the tissues, and for the solution of the colloid substances of the body, scarcely participates *in the secretion by the kidneys.* On the other hand, any excess is rapidly removed as in the case of increased supply of water. At the same time the per-centage of solid bodies in the urine sinks, so that the latter is very considerably diluted when much water is drunk. In the meantime, the water rapidly makes its way through the skin and lungs, and it is consequently desirable rather to choose dilute solutions of salt when the object is to make the urine less concentrated as regards its usual constituents, *e.g.*, uric acid.

The increased absorption and secretion of water is associated with the *occurrence of an absolute increase in the nitrogenous metabolic products in the urine.* According to experiments on man, the amount of sulphuric acid also increases in proportion to the excretion of uric acid (Genth). Hence in reality there is increased formation of these products in consequence of the greater disintegration of albumen, and not merely a washing out of the tissues, and an increased excretion of ready formed metabolic products. It is true that this *influence* of water upon the metabolism is but transient. The increased metabolism of urea even ceases after a short time in spite of the continued and copious administration of water (J. Mayer, Oppenheim). Urea appears in greater quantity even when the volume of urine increases temporarily, in consequence of the diminution of other secretions (Kaupp).

The foregoing facts indicate that ultimately the *nitrogenous equilibrium is restored*, even after a copious passage of water through the organism, but under these conditions the store of nitrogenous material in the tissue is less than it was before, when only a moderate quantity of water was taken up. If such a change occurs in the normal state of the tissues, it may be assumed that under the methodical use of pure water, in the forms of so-called indifferent warm and cold springs, *pathological products* succumb more readily to this influence, and in consequence are readily absorbed, supposing they be really capable of retrogression. From this there further follows that success is not to be expected from water cures in every case. The special indications rest upon a purely empirical basis.

2. THE CHLORIDE OF SODIUM GROUP.

(*Including the easily absorbed salts of the alkalies.*)

All substances which are very soluble in water penetrate with ease, when in the dissolved state, into the tissues of the living body, and with corresponding facility become absorbed from the stomach and intestinal canal, and are presently removed without exercising any strong and special efforts upon the muscles, nerves, or other organs. They evoke changes in the body which are essentially dependent upon the chemical relationship of these substances to the water. Since it is almost exclusively salts of the alkalies which more particularly answer to these demands, we can forthwith indicate the action in question as a *saline action*. In its purest form this only occurs after the use of the chloride of sodium, while the rest of the salts *act* more or less in *their own way* upon the various parts of the nervous system, and upon the muscles. The action upon these organic regions depends either upon the base or upon the acid, or, as in iodide of potassium, on both constituents at once. In the case of the acid salts, the action of the acid comes also into consideration, and in the case of the salts which have an alkaline reaction, the action of the alkali comes on.

To the neutral salts which are readily absorbed belong the chlorides, bromides, iodides, nitrates, chlorates, bromates, and iodates of the alkalies, and of ammonia.

The corresponding compounds of the alkaline earths pass far less easily into the blood. Sulphates are absorbed only with the greatest difficulty. In this respect the phosphates come next, while of the salts of the organic acids, as far as yet known, only the acid tartrate of the alkalies approach the sulphates.

Besides *chloride of sodium* itself, the only other members of this group which are of practical importance are more particularly the *chloride*, *bromide*, *and iodide* of potassium, as well as *chlorate of potash*, and, to a certain degree also, the analogous compounds with sodium.

Nitrate of potash has at present almost entirely lost its former great importance.

a. *The Saline Action.*

Salts and their more concentrated solutions abstract water from the living tissues, just as from every other moist body. Thereby, when belonging to the chloride of sodium group, they penetrate in large quantities into the tissue, and act upon it either as a solvent or as a foreign body which is in a state of molecular division. Through these two factors irritation results at the place of application, and it may be either functional or purely nutritive, according to the nature of the tissues influenced.

The solution of salts are consequently *local irritants*, and as such are much employed in connection with the external skin and the mucous membrane of the stomach and intestinal canal.

The chloride of sodium spring brines and lyes, as well as sea water, serve in the *form of baths* as cutaneous stimulants in all kinds of cases. Since in consequence of the resistance of the epidermis, the action is rather a superficial one, and never reaches great intensity, one can continue the use of these baths for weeks and months without having any fear of injury to the skin, which is so liable to occur under these conditions with the use of many other remedies.

The importance of salt baths rests entirely upon these effects. The separate constituents are quite indifferent, and no other kind of action is therefore imaginable, because the salts are not in the slightest degree absorbed from the watery solution by the skin when perfectly sound.

On the *mucous membrane* the salts of this group cause a far stronger stimulation than upon the external skin. In large doses they may even evoke gastritic and enteritic symptoms. This is particularly liable to occur with saltpetre.

The *lighter degrees of the saline action* can be of assistance in the various morbid states of the stomach. The collapse of the functions of the stomach, which always occurs after the use of large quantities of alcoholic drinks, is more readily removed by strongly *salted food* than by a non-stimulant diet. In chronic ailments of the stomach, the medicinal use of the chloride of sodium springs is in many cases of benefit. The special characteristic of the saline action, as compared with the other stimulants, is to be sought in the fact that the saline solution penetrates, as it were, in a full stream deep into the layers of the mucous membrane of the stomach, and the state of nutrition of the latter is favourably influenced in consequence of a constant nutritive stimulation which does not overstep a definite boundary.

Upon the abstraction of water depends the well-known *preservative property of salt.* When meat is salted, the water comes out of it in the form of a pickle, having been changed into a solution, and when thus united with the salt is no longer in the condition to aid putrefactive processes. As local antiseptics in disease, only salts which are with difficulty absorbed and have an alkaline reaction can be advantageously made use of, *i.e.*, borax, and soluble silicate of soda or waterglass.

The *consequences of the passage of the saline constituents into the blood* have only been investigated in the case of common salt. The results after this are at first more or less *thirst*, the origin of which is to be sought in the fact that the tissues give off water to the more concentrated saline solutions, and that the water is no longer able to fulfil the purposes of the organism, even while still present in it. Consequently thirst comes on before the resulting dilute solution of salt has left the body. It is, so to say, a foreign constituent in the latter, and therefore is eliminated through the kidneys. Hence an increased supply of chloride of sodium and other salts, more particularly those of the alkalies, cause an increased *elimination of water.* They act, therefore, as *diuretics.*

In *cases of dropsy* not due to disturbances of the circulation, but which have their origin in altered states of nutrition of the tissues, salts are usually preferred to other diuretics. The beneficial effect is not to be sought in increased elimination of water, because the loss is at once replaced by the solid and liquid food taken.

We must believe, consequently, that such dropsies, when not the result of renal disease, depend upon an increased tendency on the part of the tissues to swell up, and that this is influenced in a beneficial way by the action of the salts.

Just as pure water, so the salts—especially, perhaps, in consequence of the augmented secretion of the former—cause *increase* of *metabolism.* At any rate, the quantity of *urea* formed and shed after taking common salt is increased in man (Kaupp, Rabuteau) and in dogs (Bischoff, Voit). Salt acts in this way just as water, and both do so probably through their favouring the *current of the fluid of the parenchyma* through the tissues (Voit). This increased current will, *vice versa,* occur if, when the water taken remains the same, the amount of common salt in the body is subjected to a sudden reduction in consequence of the stoppage of the usual supply. Hence it seems intelligible that the excretion of urea is also increased under these conditions (Klein and Verson).

After giving the salts of the alkalies, not only does *the compound administered pass into the urine*, but other salts also appear in it in increased quantity. A supply of soda salts causes an increased excretion of potassium by the urine (Boecker, Buchheim, and Reinson). The reverse case is, however, specially interesting.

If those salts of alkalies which contain neither chlorine nor sodium get into the blood, a certain amount of *double decomposition takes place between their constituents and those of the chloride of sodium.* When phosphate or carbonate of potash are taken, there consequently results from the former chloride of potassium and phosphate of soda, and out of the latter chloride of potassium and carbonate of soda.

These *newly formed salts are superfluous* for the organism, and consequently pass into the urine with the unchanged residue of the phosphates or carbonate supplied, so that, therefore, considerable quantities of chlorine and sodium arising from the common salt are, under these conditions, abstracted from the body (Bunge) ; yet the increased excretion of sodium under a continued supply of potassium salts is only transient, and is not noticed when the supply of sodium salts in the organism is small (Gaehtgens, Kurtz).

Hence, during vegetable diet rich in potassium salts, it may be *necessary* to take *common salt with the food.* This is the case with herbivorous animals, and all races which feed entirely upon vegetables, while pastoral and fishing races hardly feel the need of common salt (Bunge).

Since the excretion of sodium ceases when the organism contains but little of the common salt, as these herbivorous animals may live without any material prejudice to health, though they are taking *no chloride of sodium with their food, so rich in potassium ;* yet experience with domestic animals shows that under the administration of common salt the state of nutrition is eminently more satisfactory.

Since in consequence of such a double decomposition more salt comes into action and is excreted than was supplied, it must be granted that the influence of the salts of potash upon metabolism and upon the passage of water into the urine is greater than that of an equivalent amount of common salt. This condition makes it intelligible that *compounds of potassium are preferred as diuretics*, and that these, especially in the form of iodide of potassium, play so important a part in the treatment of nutritional disturbances.

Of the *actions which the individual components of those salts cause on their own account*, these are of special importance which follow the use of the compounds of potassium, and of the iodides, bromides, and chlorates of all the alkaline metals.

b. *The Action of Potassium.*

As compared with common salt, chloride of potassium possesses independent actions which affect the central nervous system and the muscles, and which can be shown with all soluble compounds of potassium in case they be not overshadowed by still more powerful actions on the part of special constituents, *e.g.*, those of oxalic acid in the oxalates.

In *frogs chloride of potassium* causes paralysis of the central nervous system and heart, as well as diminution of irritability and working power of muscles. After subcutaneous injection of it into a *mammal*, death ensues through paralysis of the heart, but only when the doses exceed 1 g. per kilo. (7 grs. per lb.). When injected into the blood, quantities which correspond to about 6 or 7 mg. of potassium per kilo. ($= \frac{1}{20} - \frac{1}{15}$ per lb.) (Aubert) suffice. Doses which contain less than half of this amount of potassium cause under these conditions slowing of the pulse and transitory oscillation of the blood-pressure, either at first a fall and then a rise, or from the very first the latter (Aubert).

When administered by the mouth the effects of potassium due to absorption cannot be demonstrated, because small doses of the potassium salts are just as rapidly shed as they are taken up, so that they never come to a sufficient accumulation in the blood.

Relatively large doses readily cause *gastro-enteritis* through the local saline action, and this may result fatally. Whether in the human subject it is possible, by means of a systematic use of potassium salts, to lessen a morbidly increased *reflex irritability* and a lengthened *general sensitiveness*, does not seem quite clear. An influence upon the *action of the heart* after the taking of these salts cannot be shown to exist (Bunge). At any rate, the combinations of potassium which occur in large quantity in the food and beverages—*e.g.*, wine, Liebig's extract of meat, and potatoes—have no importance as stimulants of the cardiac action; and they have just as little value at the bedside, if they are given with the intention of *lessening a fever* temperature by moderating the action of the heart.

In former times it was customary to employ nitre for this purpose, but certainly only for the reason that it had a cool taste. Iodide of potassium has been employed latterly as a febrifuge from other considerations.

c. *Actions of the Iodides.*

The question whether *iodide of sodium* evokes actions of its own, as compared with the chloride of sodium, and yet not due to the appearance of free iodine in the organism, cannot yet be answered with certainty.

Upon an average dogs die in twenty-four hours with symptoms of dyspnœa and narcosis. If we inject into their veins 0·7 – 0·8 g. iodide of potassium per k. (5 – 6 grs. per lb.) of body weight (Böhm and Berg), the *post mortem* examination reveals œdema of the lung and pleuritic exudations. In frogs iodide of potassium causes a peculiar twitching of the muscles.

Free iodine seems to appear only in certain localities of the body *after the inception of iodine.* According to the investigations of Buchheim and Sartisson, it may be accepted as correct that this is the origin of the catarrhs of the mucous membrane of the throat and nose (*iodism*), as well as of the skin eruptions, which often are observed after the use of iodide of potassium.

On the former localities iodine is set free from the iodides which are poured out in large quantities with the saliva. This is due to the great action of carbonic acid on iodide of potassium, and on the nitrates contained in the saliva. Starch, when it contains nitrates, becomes rapidly blue, if a stream of carbonic acid be sent through it.

On the *skin* the iodides probably suffer decomposition by means of the acid contents of the sebaceous and sudorific glands, at first probably only with the appearance of hydriodic acid. This readily yields iodine and causes the eruption. The same acid is probably also to be found in the stomach when iodide of potassium has been taken. Buchheim and Strauch were, it is true, not able to find it, but this is probably due to the fact that hydriodic acid becomes decomposed, and that the iodine which then appears is united to albumen, and in this form cannot be directly tested for.

There has been much discussion as to the possibility of the *appearance of free iodine in the blood* and tissues after the use of iodide of potassium, but positive proof is as yet wanting.

The *way in which iodine is excreted after the use of iodide of potassium* seems to offer the only ground for the belief that iodine is set free in the body, and then acts irritantly upon the tissues, especially the walls of the vessels (Buchheim), just as it does when it is directly applied. The main bulk of it is rapidly got rid of through the urine, the saliva, the perspiration, and other secretions (Lewald); seven weeks after the last dose of iodide of potassium, however, traces of it are to be found in the saliva, but not in the urine (Cl. Bernard). This fact is most simply explained by assuming the presence in the organism of albumens containing iodine, and these are only able to enter into those secretions which, like the saliva, contain albuminous materials.

Of the iodides, *iodide of potassium* is by far the most employed, this being chiefly in hypertrophies due to syphilis, in exudative inflammations, in rheumatic affections, glandular swellings, especially goitre, and other similar conditions.

Before judging of the action of this remedy, we must above all remember that, on the one hand, such pathological products by no means always undergo retrogression under the use of this remedy, and, on the other hand, they not unfrequently heal even without it: that iodide of potassium in many cases helps the cure may be considered settled. These facts lead to the conclusion that the curative results after the use of this salt are not dependent upon specific actions of the same upon definite organs, and constituents of the organs, but upon alterations of the metabolism and nutritive processes. The latter need not necessarily be observable in the healthy state of the body, at any rate not as increase or diminution in the excretion of urea during a short space of time. Its importance consists probably in the fact that at first only the less stable pathological products are drawn within reach of the metabolism.

Iodide of potassium, unlike any other salts, causes a *whole series of actions.* It is rapidly absorbed, penetrates readily into all the tissues, and undergoes double decomposition with the chloride of sodium. In consequence of this its saline action must be particularly strong, when we further consider that along with the potassium and a special iodide action, which also possibly extends to the seat of the metabolism, the iodine set free can exert a direct influence upon the tissues. A sufficient basis is afforded in these conditions upon which to explain the activity of the compounds of iodine. It is true that we must leave it at present undecided whether only one of these actions is in operation, or whether all are in play at once. The latter seems not improbable, because the iodide of potassium cannot be suitably replaced in the treatment of the morbid condition mentioned, either by another iodide, or by another salt of potassium, or even by the easily absorbed salts in general.

Judging from the fact that animals can stand 0·03 g. per kg. (= ¼ gr. per lb.) iodide of potassium daily, without disturbance of their health, and judging further from experience in the human subject, the latter can take this drug in doses of 2 g. (30 grains) daily without disturbance of the nutrition due to a local action upon the stomach.

In giving iodide of potassium, it is well to give carbonate of soda with it, in order to prevent it decomposing in the acid gastric juice.

d. *The Actions of the Bromides.*

Bromide of potassium is employed in diseases of the nervous system to tone down a morbidly increased irritability of the sensory and motor areas of the brain, and by means of this, on the one hand, remove sleeplessness, and, on the other hand, to prevent the occurrence of spasmodic symptoms, more especially in the form of epileptic attacks. According to the statements of many observers, these effects of the remedy are not to be doubted. On the other hand, the question has not been with any degree of certainty answered, whether it is the potassium or whether it is the bromine that acts. The participation of bromine in the action seems from the outset improbable.

In experiments with *bromide of potassium on mammals*, only the potassium effect has been seen, while the *bromide of sodium* acted exactly as common salt.

Experiments on *healthy human subjects* yielded dissimilar results. Some observed after bromide of potassium the same appearances as after chloride of potassium (Saison). Others ascribe to the former salt special effects not due to the potassium, and which consequently appear after the use of bromide of sodium, but not after that of chloride of potassium (Krosz, 1876). These *symptoms* consist in weariness, lassitude, drowsiness, depression of the thinking power and of mental acuteness, obstruction to speech, and blunting of the reflex sensibility of the palate.

Moreover, the observations on the *sick*, especially on *epileptics*, did not lead to any unanimity in the accounts given. The absence of epileptic attacks after the use of bromide of potassium is confirmed by all observers ; but the attack usually comes back after the cessation of its administration. Yet actual cures have been noted (Begbie, Bennett, Voisin).

In regard to the *remaining bromides and salts of potassium* in general, *bromide of potassium*, according to the statements of most observers, is not excelled by any other. Yet *chloride of potassium* itself has been found sufficient. Some even ascribe to it the same importance as to bromide of potassium (Sander). According to others, it only exerts a slight influence upon the epileptic attacks, or even increases them (Stark). As regards *bromide of sodium*, most observers agree that this compound, like bromide of potassium, can prevent the excess of the attacks in epileptics, but possibly to a less degree.

Much the same is true as regards the use of the *individual salts* in nervous *sleeplessness* and general reflex sensitiveness; only in these cases it is still more difficult to arrive at a correct judgment, because the most various psychical factors exert a great influence upon the access of sleep, and may cause quite inert substances to seem to have narcotic action (Amburger).

If what has been said be once more considered as a whole, it will be seen that a *bromide action—i.e.*, the special action of bromine in its salts—is *only* clearly *noticeable in man*, especially in the treatment of epilepsy and nervous states of excitement.

Moreover, the *symptoms of poisoning* which not unfrequently occur after the continued use of *bromide of potassium* and *bromide of sodium*, and which cease after the stoppage of the remedy, argue in favour of an independent bromine action, so far as the brain is concerned. These *cerebral symptoms* are loss of memory, weakness of sight and hearing, lowering of sensitiveness of the skin, unsteady gait, stupor, delirium, and maniacal attacks. On the other hand, the symptoms in the *stomach and intestine* observed in such cases are to be referred to a local action, and the general nutritive disturbances, such as *anæmia and wasting*, are to be considered as the results of the disturbance of nutrition. Probably, too, the action of the salt upon metabolism plays a part in this: the *slowing of the pulse*, which is not seen after the use of the bromide of sodium, depends probably upon the potassium. Finally also, the bromides, like the iodides of potassium, cause *skin eruptions* in the form of acne pimples and pustules, as well as *catarrhal conditions of the mucous membranes.* Of the latter, the respiratory mucous membrane seems at times affected, at any rate after the use of bromide of potassium. Violent fits of coughing in women and children are often noticed.

e. *The Action of the Chlorates.*

The actions of these salts correspond to that of the chlorides. It is only where the conditions for their *dissociation* in the organism are afforded that the oxidising action of the *chloric acid* comes into consideration. The undoubtedly favourable result, after the use of chlorate of potash in various *affections* of the *mouth and throat*, is to be referred to the local disinfectant nature of the saline action.

Probably in the mouth, through the action of the great quantity of carbonic acid and through that of other acids which are occasionally present, a small quantity of the chloric acid is dissociated, and this is important as a disinfectant.

This salt is given internally in mouth affections. After its absorption it becomes *excreted*, at least for the greater part *unchanged*, with the urine and other secretions (Isambert, Rabuteau). It also passes into the secretions of the mouth, and at the same time it probably comes into contact with those parts which it does not reach when only applied locally.

After the internal use of large doses in certain cases, especially in children, *severe symptoms of poisoning, and even death*, have been known to occur. These harmful results are due to the alteration of the oxyhæmoglobin into methæmoglobin through the oxidising action of the chloric acid (Marchand). The blood herewith assumes a chocolate colour, and loses its power to yield up oxygen, the corpuscles swell and surrender their colouring matter to the plasma, and finally turn into a gelatinous mass. The *symptoms* and *pathological appearances* observed depend upon these changes. These are hæmaturia, reduction of the urinary secretion, blood casts in the canals of the renal pyramids, discoloration of the skin, also icteric and general ailments, which may lead to death by coma or convulsions.

The acetates of potash and soda, their citrates, &c., may be included with the above, because of the saline action, but seeing that in the blood they change into carbonates, they must be specially discussed with the carbonates subsequently.

3. The Glauber's Salt Group, or that of the slowly absorbed Aperient Salts of the Alkalies, of the Alkaline Earths and of the Earths proper.

To this group belong all chemical compounds which are easily soluble in water, which are only with difficulty absorbed in the intestinal canal, and are pharmacologically indifferent, except as regards those actions which are dependent on the properties indicated, be these substances organic or inorganic in their nature. The typical members of the group are *Glauber's salt* and *Epsom salt.* Closely related to these are various compounds of magnesia, some few *phosphates and tartrates* of the alkaline metals, and among the non-official salts ferro-cyanide of potassium, and sulpho-vinates of the alkalies. Of the organic compounds, *Mannite* is worthy of being mentioned.

On account of their disinclination to pass through membranes by endosmosis, the substances of this category permeate only with difficulty into the tissues, and therefore cause no appreciable irritation of the skin or mucous membranes. In the intestine they are absorbed with difficulty, and hence their solutions reach the large intestine and prevent consolidation of the fæcal masses, which are consequently ejected in the fluid condition along with the greater part of the salt. Although these salts do not excite inflammation of the sensitive mucous membrane, the gentle stimulation that they cause suffices to strengthen the peristalsis and to favour the evacuation of the fæces in the fluid state.

The idea that the aperient salts cause a *transudation out of the blood* into the intestine by *abstracting water* (Liebig), is contradicted by the facts that Glauber's salt brought into a Thiry's intestinal fistula causes no accumulation in it (Thiry, Schiff, Radziejewski), and that the concentration of the saline solution has no influence as regards the action (Buchheim).

If the purgation were caused by a transudation from the blood into the intestine, the action would increase with the *concentration of the solution*, and salts administered without water would cause severe diarrhœa. Yet that is not the case. If we give Glauber's salt in substance to animals whose digestive canal is free of fluid, no evacuation occurs after an otherwise sufficient quantity. The salts under these conditions become gradually absorbed, yet by employing a concentrated solution, an increase of the secretion, and to a certain degree an increase of the quantity of intestinal fluid, are quite feasible (Hay).

A real transudation only takes place when we open the abdomen and insert the salts into a ligatured loop of intestine. In this case the inflammatory processes due to the operation assist in causing the secretion. Hence the irritant effects of the salts of the chloride of sodium group and phosphate of soda, even in uninjured animals—at least in rabbits—cause a great effusion of fluid into the intestinal canal (Bunge).

The *blood* in man and animals becomes *richer in red corpuscles* after Glauber's salt has been taken (Hay). The cause of this concentration is not so much to be sought for in the above-mentioned increase of intestinal secretions, as in the deficient replacement of the water lost through the skin, lungs, and kidneys, in consequence of the prevention of the absorption in the intestinal canal.

It has been also assumed that the aperient action of the salts of this group, after their passage into the blood, takes place through *irritation of the intestinal nerves, and acceleration of the peristalsis.* This view, however, is contradicted by the fact that after the injection of Glauber's salt into the blood the fæcal matters no longer get more fluid, but, on the contrary, assume a firmer consistency, because of the increased abstraction of water through the kidneys when the salts are excreted.

Carbonate of magnesium and *magnesia usta* also act as aperients, because, through the carbonic acid present in the intestinal canal, they are converted there into the relatively soluble and very slowly absorbable *double carbonate* (Buchheim and his school). All the salts of magnesium pass into the carbonate by double decomposition with the carbonate of soda in the intestine. In the process of absorption each of the resulting salts follows its own rule.

Consequently, if Epsom salts be taken, as compared with the sulphuric acid, more magnesium is passed by the fæces than the urine, and, *vice versa*, more sulphuric acid appears in the urine than represents the increase in the amount of magnesium in it (Aubert, Buchheim and Kerkovius).

That the aperient salts are with difficulty absorbed, is proved by the small quantity of them which passes into the urine. The longer, however, they linger in the intestinal canal, *e.g.*, when one suppresses the evacuation by morphia or tannin (Buchheim), or employ only a small quantity of the salt in but little water, so much the more copiously does absorption follow. Consequently, after small doses of the double tartrate of sodium and potassium (Seignette salt), the urine regularly assumes an alkaline reaction, but after large doses only when no diarrhœa occurs (Laveran and Millon, 1844). Upon the like conditions rests the fact that the rabbit through the greater length of its intestine absorbs ten times as much phosphate of calcium and magnesium as does the dog. These salts it excretes with the urine (Buchheim and Körber).

From this method of action on the part of the saline aperients, many rules can be deduced for their employment in practice. First of all, it is better to give them in fairly dilute solutions than in concentrated ones, or than as a powder. Hence the naturally bitter waters are very suitable, but it is a matter of no consequence that one is somewhat more concentrated than the other, or that it possesses a greater or less quantity of accessory substances, such as the salts of lime. Yet the advertisements which puff up the various mineral waters, as a rule, lay great stress upon that fact.

If large quantities of saline solutions linger a long time in the *stomach,* they are prone to *cause disturbances* of its *functions.* Hence the saline aperients are only to be used with caution in the case of patients who lie continually in bed; especially must their frequent employment kept up for a long time be avoided, because in rest and in the horizontal position the passage of the contents of the stomach into the intestine is impeded. In other cases we must take care that the solutions of salt leave the stomach as soon as possible. This is the object of the customary walk which the bath physicians prescribe to the patients after each drink. When therapeutically employed, if the aperient mineral water is continued for days and weeks, the object aimed at is mainly to be sought in the fact that in the intestine fermentative and putrefactive processes occur, even under ordinary circumstances, and sometimes in disease, to an increased degree, and that it gets, as it were, flushed out and disinfected by the copious supply of aperient waters, and the regular and thorough removal of its contents.

Since the aperient salts only cause slight irritation, they may be used in those cases where the object is to empty the intestine in inflammatory and other febrile diseases without irritating it, because otherwise the fever might be increased. The old idea of the *antiphlogistic action* of the neutral salts is to be associated with those negative properties, any favourable effect upon the inflammation and upon the fever can only be attributed to this evacuation of the bowels. In this process there probably results an increased flow of blood to the intestine, and through this a determination of blood to the affected organ, *e.g.*, the lung, is lessened, and the course of the ailment is influenced in a favourable manner.

If, however, the *intestinal canal* itself be the *seat of an inflammatory affection*, the slight irritation which Glauber's and Epsom salts induce suffice to increase the inflammation. Hence in such cases we give the preference to other remedies, *e.g.*, calomel. *The combination of the aperient salts* with such remedies as act by increasing the peristalsis is not injudicious. Of these, senna is especially useful, because it apparently excites only the intestinal ganglia, without causing inflammation. For that reason the black draught is a very rational aperient.

It may be remarked here that the senna leaves may be freed from their unpleasantly bitter and rasping constituents by first extracting them with alcohol, for after this they retain their efficiency.

Tamarind pulp and extract of *Triticum repens*, as well as *prunes*, and *elder pulp*, contain acid organic salts of the alkalies, and their aperient action is probably increased by the presence of colloid substances. *Whey*, also, is to be included here. It is made by means of essence of rennet (*Liquor seriparus*), or with 1 per cent. of cream of tartar (*Serum lactis dulce et acidum*), and frequently receives the addition of tamarind pulp (*S. lactis tamarindinatum*).

In the case of mannite, which belongs here, the gummy colloids present in it probably aid its passage to the intestine, and so assist the aperient action.

CHAPTER IV.

CHEMICAL CAUTERISATION BY MEANS OF ALKALIES, ACIDS, HALOGENS, AND OXIDISING SUBSTANCES.

In contradistinction to the molecular actions of the agents hitherto treated of, the alkalies, acids, halogens, and stronger oxidising agents cause *peculiar chemical changes in the constituents of the tissues.* These receive the name of cauterisation. This begins with the slightest alteration of the protoplasm, which cannot be analysed, and ends with a perfect transformation and decomposition of all the substances of which the tissues are composed. The results consist in inflammation or destruction in the latter case, with corresponding loss of substance (surgical cauterisation.)

The altered constituents of the tissues, their decomposition products, their plastic exudations, as well as the compounds of all these substances, with the components of the caustic, form a mass which is called the "*Eschar.*" This has either a soft consistency, and is only loosely attached to the subjacent unaltered tissue, or it consists of a tenacious, dry, firmly adherent mass.

The *loss of substance* can also be brought about through the *tissue* not being directly *destroyed*, but *killed*, and *then thrown* off as a slough, or that it collapses through destructive inflammation. The caustic action which immediately brings about the destruction is always accompanied by inflammation of the neighbouring parts. On the other hand, the latter may come on without destruction of the tissue, if the quantity of the caustic and the duration of the action do not overstep certain limits.

All the elementary tissues, connective tissue, cellular elements, the walls of the vessels, the blood, and the nerves, are more or less simultaneously attacked by the *caustic action.*

In its milder degrees, as after the application of media which have a molecular action, we have often to do only with the *sensory irritation*, and with the active congestions at the point of application, which are dependent upon the *dilatation of the vessels.* The next degree of the caustic action causes the different *inflammatory processes*, with or without the formation of blisters on the skin, the appearance of false membrane on the serous and mucous surfaces, of parenchymatous swelling, cloudiness, and tumefaction of the cellular elements.

Even the *course and the results* of the inflammation caused by the caustic action present no peculiarities. The latter can in the lighter degrees retrogress, and in the severer, pass on to destruction, suppuration, and dissolution of the tissues.

The *toxical importance* of many chemical compounds rests merely upon the fact that they induce *gastro-enteritis*, through cauterisation of the mucous membrane of the stomach or intestine, or cause chronic catarrhal affections when applied for a long time in small quantity.

When *caustic agents are employed in therapeutics*, we seek either, by means of stimulation of the nutrition, to cause hypertrophies to retrogress, and to bring exudations to absorption (p. 102), or we endeavour by stronger cauterisation to destroy and clear away pathological new formations, and morbidly altered tissues. The *alkalies* have, moreover, the property of softening horny growths, of dissolving mucus, of emulsifying fat, and of causing connective tissue to swell up.

In the case of the *acids and alkalies*, *the property which* these have of *mutually neutralising each other* also comes into consideration.

Wherever acids are normally present, as in the stomach, or wherever an acid reaction is found, as in the urine, we can, by neutralising this, exercise a material influence upon the functions and states of the organ concerned. *Removal of normal alkaline reactions of the tissues* is of itself sufficient to cause disturbance of nutrition and function of the structures in question.

All organs, especially those of the nervous system, are during life *continually* under the *influence of an alkaline* reaction, which is entirely, or at any rate predominantly, caused by carbonate of soda. The nature of this influence is as yet unknown: we only know that its absence infallibly causes death. When the alkalies in the blood of a rabbit are neutralised by giving hydrochloric acid by the mouth, the animal dies before total neutralisation of the alkaline reaction of the blood occurs, and therefore at a time when a direct acid action upon the nervous system, or upon the other organs, is out of the question. Hence it is a matter only of the *reduction of the normal alkaline action.* Since, to begin with, it seems possible to strengthen the latter by giving carbonate of soda, the difference between the action of acids and of alkalies, after their reception into the blood and tissues, is to be considered exclusively as quantitative. In favourable cases the *carbonate of soda strengthens the normal alkaline reaction*, while the mineral acids, under certain conditions, lower it. Hence in this sense there is no such thing as an independent acid action.

The action of the *oxidising agents* and of the free halogens remains almost entirely restricted to the place of application. The exceptional position taken by iodine in this respect will be specially referred to.

In the *employment of escharotics for therapeutic purposes*, it is not a matter of the specific action of the remedy, but of the nature and degree of the caustic action. The alterations of the nutritive processes in the tissues caused by the latter are in such cases the curative factor. Experience teaches that, besides the reflex actions (p. 103), under the influence of a lasting local irritation morbid products are in certain cases absorbed. The discussion of the nature of these processes belongs to general pathological physiology.

In accordance with this state of affairs, it is in itself *a matter of indifference through what remedy the curative agency is evoked.* On the other hand, it is of great importance that this action be produced in every case to the requisite extent over a sufficient area, and for a long enough time. To estimate these conditions correctly, and to choose a remedy suitable for effecting them, is the important task of the medical art, the solution of which task is afforded by an exact knowledge of the properties and actions of escharotics.

We have to do with similar but more simple conditions in the destruction, or *surgical cauterisation*, of morbid tissue and pathological new growths. Here very much depends upon the area to be destroyed, and the choice of a suitable agent.

1. THE ALKALI GROUP.

To this belong all the compounds of metals of the alkalies and of the earths which possess basic properties (alkaline reaction), and which contain no components which exert a peculiar action. The *hydrates*, *the carbonates*, *the basic phosphates*, *borax*, *and the salts of the fatty acids* (*soaps*), answer these claims. In the case of the alkaline cyanides of potassium, only the prussic acid action comes into consideration, and it must therefore be excluded from this group.

The *hydrates of the alkali* metals are strong caustics. Among them, *hydrate of potash*, or *caustic potash*, is made use of in the familiar form of rods for surgical purposes. Its violent, destructive power is due to its abstracting water, as well as to its dissolving and breaking up the tissue-forming constituents of the body. The eschar formed is deliquescent, like the remedy itself, and offers no hindrance to the further penetration of the potash into the tissue. The caustic effect has, therefore, usually considerable depth, and readily extends into the neighbouring parts, because of the deliquescence of the remedy. In order to prevent this, it is usual to mix the caustic potash with an equal quantity of caustic lime (Vienna paste), or to melt two parts of the former with one of the latter (Filhos' caustic).

In *skin diseases hydrate of potash* is used in the form of more or less dilute solutions, for the purpose of inducing a moderate degree of cauterisation over a large surface.

Caustic lime, because of its low price, is suitable as a *powerful disinfectant* for the wholesale destruction of organic substances, especially animal products, when they accumulate in places from which it is difficult to get them removed; the only means left for preventing them putrefying, and for causing their rapid decomposition without the intervention of ill-smelling and harmful products, is to mix and cover them over with a sufficiency of caustic lime. This is, as a rule, the easiest way to disinfect large common graves in epidemics and after battles, so also slaughter-houses, latrines, cellars coated with mud, and other localities.

Soaps and the alkaline carbonates, especially the former, are used for cleansing the skin, as is well-known. They emulsify the fat of the skin, and soften the superficial layers of the epidermis, so these are removed with all adherent impurities by rubbing and by the rinsing. A similar influence is exerted by the *alkaline baths*, which are employed methodically in the form of mineral waters, or solutions of potassium carbonate and sodium carbonate in skin diseases, in order to soften and dissolve the pathological products and tissues. They differ in this respect from the salt baths and brine baths which attack the epidermis less, and which are consequently chosen in these cases in which one wishes by uniform irritation to encourage especially the functions of the skin, and reflexly those of other organs.

The *behaviour of the alkalies in the stomach and intestinal canal* can, as a rule, be readily followed. If the peculiar actions are left out of consideration, it resolves itself mainly into a question of neutralisation of acids, of a solution of mucus, and presumably also of the loosening of the epithelium. The results of these alterations are more difficult to judge of.

The *neutralisation of acids in the intestinal canal* is, first of all, of importance in those catarrhal and other affections in which fermentative and putrefactive processes cause an *abnormal formation of acid.* Such forms of catarrh of the stomach and intestine are specially frequent in children. The irritation which the morbid, and therefore sensitive, mucous membrane experiences from the acid favours the occurrence of the diarrhœa so dreaded in the earliest years of life. For the neutralisation of the acids, we turn in such cases with preference to *magnesia usta,* because it offers the advantage that the aperient salts formed by it bring about a rapid evacuation of the decomposed and deleterious contents of the intestine. We seek to encourage this result by an addition of rhubarb to the magnesia (Gregory's powder). In this case the removal of the fermenting masses at the same time gets rid of an essential cause of illness.

When it is important to keep up in the intestinal canal for a long time a moderate alkaline action without evacuation, *tribasic phosphate of lime* is best adapted for the purpose, for it is carried far down into the intestine, whilst the action of the *carbonate of soda* is restricted mainly to the stomach. The importance of the latter carbonate in chronic catarrhs of the stomach is less to be ascribed to the neutralisation of the acids than to its effect in dissolving the mucus which is formed in increased quantity in such cases, and which is deposited upon the mucous membranes in thick layers because of its insolubility in the acid contents of the stomach.

Alkaline mineral waters are frequently employed for this purpose; in these, through the presence of other constituents, the saline action also comes into question (p. 119).

The carbonates, and therefore carbonate of lime or chalk, are less suitable as *neutralising agents in poisoning with acids*, because the carbonic acid, which is developed in large quantities in these cases, gradually dilates the stomach, and may easily lead to rupture of it if the caustic action should chance to extend to the deeper layers of the wall of the stomach.

But even when that is not to be feared, an increased distention of the stomach with gas must be also avoided, because, when thus dilated, it interferes with the functions of the neighbouring organs, especially the heart and lungs, which, in conditions of disease, are caused to suffer by sympathy. Since, to begin with, the hydrates of the alkalies are excluded from such applications because of their caustic action, and the basic potassium compounds yield with most acid salts, which cause a strong local irritation, the only *suitable antidotes* left *in cases of poisoning with mineral acids* are *magnesia* and the *soda soaps*. These fulfil all claims, because they themselves, and the salts formed from them, and the products of neutralisation, are as harmless as possible. In poisoning with oxalic acid, a combination of caustic lime and sugar (saccharate of lime) is a very suitable remedy (Husemann).

Magnesia is recommended in cases of poisoning with arsenic and arsenious acid, for in neutral and alkaline fluids it forms insoluble compounds with these acids, but these, however, only form readily if the magnesia has been freshly precipitated, or *not* too strongly calcined (Bussy).

An increase in the supply of alkalies causes, under all conditions, an increase in the amount of them in the whole body, even when they are neutralised by the acids of the gastric juice; for the alkaline intestinal secretion, which, under ordinary circumstances, experiences neutralisation by the gastric juice, escapes this fate, and returns unaltered into the blood. The excess thus brought about, then, is passed with the urine, and imparts to it an alkaline reaction.

Now the question arises, to what degree *does the quantity of alkali in the blood rise* under such circumstances, and what influence does such a rise exercise upon the functions and metabolic processes of the organism? In this it is, however, apparently not a matter of indifference whether increased alkalinity is brought about by carbonate of soda or by carbonate of potash. The organism is continually under the influence of the carbonate of soda action, and the absence of this at once brings about death, as experiments in administrating hydrochloric acid to rabbits show. The rabbits can in such cases be saved even just before death by injecting carbonate of soda into the veins, while carbonate of potassium or carbonate of lithium have not this curative effect, perhaps because they act in a way of their own upon the nervous system.

Of the questions above opened up, none can up to the present time be answered, even with approximate certainty.

There have been no sufficient investigations into the *neutralising power of the blood* for acids (the strength of the alkaline reaction) *after administration of alkalies*, because of the difficulty of fixing the acid equivalent of the alkali of the blood with sufficient certainty. According to experiments thus far, it seems that the amount of carbonic acid in the blood rises only to a moderate extent after the administration of carbonate of soda, so that, therefore, a noticeable accumulation of the latter in the blood cannot be assumed.

What importance such a slight increase of the soda of the blood after exclusion of all co-operative factors has upon metabolism, is totally unknown. Alterations of the latter, after the administration of alkalies as well, have been proved to take place, but in man and animals they are the effect of various factors, amongst which the influences of the increased alkalinity of the blood does not show itself clearly.

First of all come into consideration the results of *the action of alkalies upon the stomach and intestinal canal.* These may be such that digestion and absorption of the food is disturbed, and the quantity of the metabolic products reduced. The *saline action* has an opposite influence, which therefore consists in an increase of the metabolism (p. 119), and this action is possessed by the alkaline salts which come into consideration here, provided they are easily absorbed like carbonates of the alkali metals.

The *increased alkalinity* of the blood has been supposed to exert a great influence upon oxidising processes in the organism. Attemp have been made to strengthen the latter by the therapeutic use of alkalies in those cases in which the ailment was supposed to be deducible from a succumbing of the physiological combustion, as was especially supposed to occur in diabetes, and is supposed to a certain extent, even now, to exist in the case of gout. Because of the difficulty of carrying them out, investigations are wanting which distinguish, according to the individual factors, the results of the supply of alkalies upon metabolism. The statements at hand refer only to the total influence of the supply of alkali, and are, to some extent, mutually contradictory.

In general, *an increase of the secretion of the urea*, and therefore an increase of the decomposition of albumen from the use of carbonate of soda, with which most experiments were carried out, has been observed in human beings so long as the digestion remained undisturbed (Rabuteau and Constant, Martin-Damourette and Hyades). Münch found only the excretion of water increased. In the case of dogs the experiments showed sometimes an increase of the nitrogenous transformation (J. Mayer), and sometimes no notable alteration in it (Ott).

The *alkalies* are considered as specially *effective* in the *treatment of gout.* It has been usual to start with the already described assumption, that in consequence of the increased alkalinity of the blood, the *combustion of the uric acid* to urea is favoured as a matter of fact. Basham, in his experiments on patients who were suffering from uric acid calculi, arrived at the result that after the rise of alkalies uric acid disappears, while the quantity of urea increases. Mostly, however, the results of such investigations were vacillating and uncertain, or even perfectly negative (Severin). This is true also in regard to carbonate of lithia, the influence of which upon the secretion of uric acid Bosse and Buchheim examined in themselves and in gouty patients.

Not only are the alkalies given for the purpose of preventing the deposition of uric acid in the joints and in the bladder, but they are often given, too, with the idea that they will *dissolve uric acid concretions already formed in the bladder.* Carbonate of lithium has been specially recommended for this purpose, because it dissolves uric acid, and more readily than other alkalies (Lipowitz and Ure), and in four times the quantity that the same amount of carbonate of soda can do it (Binswanger). But in those cases the conditions in the bladder are not so simple that the solvent power of alkalies can play an essential part in such a method of treatment. The latter certainly pass into the urine, but in the case of human beings by no means regularly. Like all other salts, carbonates of the alkalies are shed in the kidneys in the most acid condition possible, and consequently appear in the urine as bicarbonates under these conditions; at the most, only the very insoluble acid urates form in the bladder, so that from this fact alone the purpose aimed at is frustrated. Further, we must notice that the solvent power which comes into action in a very dilute state can after all only very slightly attack large stones with a relatively small surface. If the urine, however, after the supply of very large quantities of such remedies, takes on a strong alkaline reaction, the danger comes on, that after long use a precipitate of the earthy phosphates may follow, and so afford a new source for the formation of calculi.

If, notwithstanding this, *uric acid concretions* have been *observed to be passed* after the methodical use of alkaline mineral urates, this result depends upon the fact that the stone in the bladder was not a simple solid, but was a mass composed of several small portions, cemented together more or less firmly by mucus and other substances, and this mass was caused to break down and be evacuated piece by piece through the influence of the alkali in loosening and dissolving the binding substance.

Moreover, in other morbid states of the urinary organs, the transitive alkaline nature of the urine may be of use in a manner resembling that in the digestive canal. A beneficial and *direct influence upon the mucous membrane and epithelium* of the urinary canals can, under certain circumstances, be effected in the bladder, in the pelvis of the kidneys, and probably also in the kidneys themselves. Even the neutralisation of an exceedingly acid reaction of the urine is at times therapeutically, or, at any rate, prophylactically of importance. In this case an endeavour is made in suitable cases to prevent, or at any rate restrict, the precipitation of free uric acid in the bladder, and the formation of vesical calculi.

Just as the easily diffusible salts in general cause an *increased excretion of water* by the kidneys, and consequently act as *diuretics*, so the alkalies do the same. In practice these are preferred to the neutral salts in this respect. Whether or not they in reality pass the kidneys more readily than the latter, and are therefore more powerfully diuretic, as we are inclined to believe, judging from their greater power of filtration through the animal membranes, cannot be decided for want of sufficient facts, yet the statement cannot be denied that these remedies are, as a rule, of greater use in dropsy than are the neutral salts of the alkalies. The favourable result, however, does not need to be dependent upon the diuretic action, but may with greater probability be considered as due to a favourable influence upon the state of the tissues in the manner indicated under the chloride of sodium group.

In the employment of the alkalies as *diuretics*, the potassium salts are preferred to the sodium compounds, and the predilection is mostly for acetate of potash. When carbonate of potash is administered for a long time, the repeated neutralisation of the gastric juice due to it, as well as its direct influence upon mucous membranes, render it very liable to cause disturbances of the functions of the stomach, while the acetate has not these inconveniences, and can be used without harm for a considerable time. In the body, the acetic acid is consumed like other pure organic acids of the fatty series, and the potassium appears as the carbonate which then develops the desired alkaline action.

From these organic substances arise the carbonates which are found in the urine of human beings after the consumption of vegetables and fruit; they impart to the urine of the herbivora its alkaline reaction.

The *compounds of the alkalies and the alkaline earths with sulphur*, that is, the sulphides as well as the sulpho-hydrates, are closely related to the former group as regards their local actions. They are distinguished for their great *solvent power for horny tissues*, and consequently in the Orient are used as depilatories. Through this property they are able to attack the skin, and especially the epidermis, very powerfully, and consequently are made use of in *skin diseases* in the same sense as diluted liquor potassæ, but not so frequently now as formerly. It is a matter of indifference what alkaline sulphide is chosen for this. For a long time pentasulphide of calcium was much liked in the form of *solutio Vleminx.* The idea of a specific action of these remedies upon the skin cannot for a moment be entertained. The belief that sulphur and its preparations have a special affinity for the skin has come down by tradition, and shows itself even at the present day in the use of sulphur waters, in the form of baths and drinking waters, for skin diseases, and other affections in which the skin and mucous membranes participate.

The small quantity of sulphuretted hydrogen which comes into action most certainly does not render these waters curative agents. The action of cold and warm water, the diet and the style of life led in such cases, are quite sufficient to explain the curative effects observed. Then the fact that sulphuretted hydrogen injected into the blood of a cat causes alterations of the intestinal canal (O. Weber, 1864), resembling those found in arsenical poisoning, as well as the circumstance that sulphuretted hydrogen is absorbed by the skin, are not sufficient to warrant us in ascribing any therapeutic importance to sulphur waters.

Sulphuretted hydrogen is, moreover, a nerve poison, which, without abstracting oxygen from the blood, causes paralysis of various areas of the central nervous system.

2. The Acid Group.

The pharmacologically typical acids are *sulphuric acid and hydrochloric acid.* Phosphoric acid is closely related to these. Of the others, some are distinguished by special properties, which also come into consideration in their actions. *Hydriodic acid* and *sulphurous acid* are powerful reducing agents; *nitric acid* acts in its own manner, forming the so-called xantho-proteic acid out of albuminous substances in which the nitrous group seems to occur. It cannot bring about oxidation in the organism. *Hydrofluoric acid* is distinguished by its specific caustic properties.

The organic acids of the fatty series only belong here because of their local actions, for they are more or less perfectly consumed in the body. The higher members of the fatty acids, which exert no action at the place of application, serve as food. Those acids of the series into which the halogens, the nitrous, and the sulphurous (SO_2OH) groups are instituted have not been further investigated.

The aromatic acids take a special position in more ways than one.

The caustic action which the concentrated mineral acids evoke depends very often upon an *abstraction of water.* Concentrated sulphuric acid abstracts from most organic substances not only the water already there, but abstracts hydrogen and oxygen from them with avidity under the formation of water, and therefore frequently causes *carbonification.* With the other inorganic acids the abstraction of water plays a far more subordinate part.

The *acid action* which appears in the pure form in the case of most mineral acids only when they have been to a certain degree diluted, consists in the neutralisation of the alkalies, *and a more or less energetic transformation of the tissue-forming substances*, especially of the protoplasm. As already stated in the introduction to this chapter, the removal of the alkaline reaction of the tissues through the local application of the acids seems of itself sufficient to cause inflammation and other disturbances. The main action is, however, to be referred to the alteration of the albuminous and gelatine yielding tissues. Dissolved albuminous bodies become coagulated by concentrated acids —with especial readiness by nitric acid—and are transformed into the special modification called acid albumen.

The finer changes in the protoplasm, which show themselves as a stimulation, which produce stasis or inflammation, cannot yet be referred to tangible chemical processes, so far as coagulation and neutralisation of the alkalies are not at work.

The *connective substances* experience a change under the influence of the dilute acids, especially of acetic, and of the remaining volatile members of the fatty acid series, even of ordinary temperatures, and this change indicates itself externally only as a loosening and swelling up of it. In this condition the chondrin of the connective tissue, when treated with hot water, passes into glue more readily than before the treatment with acid. Upon this rests the facts that meat acidified during the *post mortem* rigidity can be more easily boiled, and yields more tender roasts than the meat of newly slaughtered animals. In the fabrication of Sauerbraten, the aim of the so-called soaking is to make meat from old animals with tough connective tissue soft and tender through the action of vinegar. Even the *horny tissues* are very strongly attacked, softened, and dissolved, especially by the more concentrated volatile fatty acids. Even the hardest epidermis and corns cannot resist concentrated acetic and monochlor-acetic acid. On account of these above-mentioned actions upon the constituents of organised structures, the mineral acids are able to restrain the development of the lower organisms, and *to suppress putrefactive processes.* Whether *boracic acid*, which has been recommended in this direction, has special actions of this kind is uncertain.

In a considerable number of cases, the *acids* are used in practice as *caustics* and *local stimulants*, yet hardly a case can be cited to which they are quite indispensable. This is true also of the use of fuming nitric acid as a surgical caustic. The recommendation of *aqua regia*, in the form of foot-baths, for disorders of the liver and other ailments of the internal organs, descends from the time when it was the custom to consider those symptoms which were to be seen as the result of an inhalation of chlorine and nitrous acid as due to the passage of nitric acid into the blood.

Most frequently *the acids* in the dilute state are used in the form of baths, lotions, and linaments, as *mild*, *cutaneous* irritants. The volatile fatty acids are specially liked in this respect, and rank with the other volatile remedies of this kind. They are suitable in those cases in which it is necessary to obtain a gentle but not altogether superficial action without injury to the epidermis. The latter is not softened or thinned as after the application of the alkalies, but rather gets a closer structure. Hence vinegar, as compared with the ethereal oils of the turpentine group, which tend to cause renal affections after their absorption, lotions and linaments are commendable for the purpose of exciting the activity of the skin in those cases where the epidermis must be spared, *e.g.*, in feverish affections. For baths, from old habit, *formic acid* is often preferred in Germany. It was originally always obtained from ants, by making an extract of them and of their nests by means of hot water. In the latter there are contained several volatile products of the turpentine group. The extract thus made used to be employed in the form of "Ant Bath."

Acid vapours answer also for *inhalations* and for smelling, but have no advantage over other volatile substances. It is only when the inhalation is undertaken with the intention of quelling hæmor rhage in the bronchi, in the trachea, or in the nostrils, that the acids cannot be supplanted. The condition demanded is that the escaping blood should assume the acid reaction necessary to its coagulation; yet this is nevertheless difficult to fulfil, and the result is therefore an uncertain one. The stoppage of bleeding is effected far more easily in localities where the acid can be applied directly to the bleeding spot. The mineral acids act more powerfully in this respect even in the dilute state. They are, however, far excelled by those metallic salts which have an acid reaction—*e.g.*, chloride of iron.

In the use of organic acids in the form of *lemonades* and other *acid drinks*, the local action upon the organs of taste plays the chief part. These acids are in many cases important constituents of articles of luxury. The finer kinds of vegetables and fruits have an insipid and unpleasant taste if the necessary quantity of tartaric, malic, or citric acid is absent. Even in wine the connoisseur would not willingly miss a certain acidity. For the supply of cold water—*e.g.*, in feverish conditions—the acids have a similar importance to that of the "teas" (p. 93) in the administration of warm water.

The question as to the *behaviour of acids in the stomach* has a special interest from the important part hydrochloric acid plays in the digestion in the stomach.

The facts fully proved by C. Schmidt, that *hydrochloric* acid is secreted in the *stomach*, either free or loosely united with pepsin, led at the outset to the belief that disorders of the stomach are in certain cases dependent upon a deficient secretion of this acid. But, however great the attempts were to employ hydrochloric acid in the treatment of affections of the stomach, certain results were not as a rule to be obtained, because only in quite recent times has a start been made to establish the pathology of the excretion of hydrochloric acid upon the basis of exact investigation. The great difficulties which present themselves in this undertaking have not been yet sufficiently overcome. Accordingly the indications for the employment of hydrochloric acid rest for the present more upon empirical than upon rational foundations. The details of this belong to special pathology.

The *stomach* in normal conditions is almost always under the influence of the action of an acid. A moderate increase of this, by the inception of acids other than carbonic acid, has therapeutically no special importance. After the continual use of acid drinks, as for instance the customary consumption of acid wines, chronic catarrhs of the stomach are prone to occur.

The abnormal *formation of acids* due to *fermentative processes*, met with typically in the diarrhœa of little children, already spoken of, proves very especially injurious to the mucous membrane of the stomach and intestines. In these cases the acid contents of the stomach cause the transformation of the bilirubin into biliverdin, and in consequence of this the well-known green colour of the fæces, so dreaded by every mother. The treatment of this condition aims at the neutralising of the acids and the removal of the fermenting and decomposing mass.

The *neutralisation of alkalies* which have reached the stomach in cases of poisoning, follows the same general rules as in the case of the acids. In neither case must the remedy employed or the products formed be injurious. Besides the inorganic acids, of which nitric alone is inapplicable, a great number of organic ones are at our disposal, more particularly citric and tartaric acids.

Carbonic acid also takes a special position pharmacologically, in the form of carbonic acid waters. It is not only a very favourite beverage, but at the same time an active remedy for catarrhal states, and in the trifling complaints and slighter troubles of the stomach, which frequently occur after immoderation in eating and drinking. The explanation of the curative effects of the gaseous acid is to be sought in the fact that it retains its activity even in the presence of alkalies. It penetrates the walls of the stomach in all directions, and does not then become, like other acids, entirely neutralised in the tissues, but when present in sufficient quantity, it is there simultaneously as bicarbonates and in the absorbed state. In this way carbonic acid can stimulate the functions of the tissues without interfering with the essential properties of the alkalies. In addition to this there is another factor, viz., that the stimulation always remains moderate, and consequently can never injure by excess.

Carbonic acid also gains special importance because it *favours the absorption of water in the digestive canal.* When the water contains carbonic acid, the time which elapses from its reception to its excretion by the kidneys is shorter, or, in other words, its passage through the body becomes accelerated (Quincke). The carbonic acid waters are consequently, in this sense, more powerful diuretics than common water, and probably strengthen the action of the latter upon the metabolism.

In contradistinction to the stomach, the intestine is almost always under the influence of alkaline contents. When the latter become acid in reaction, in consequence of abnormal formation of acid, or after the passage of the acid contents of the stomach into the intestine, then this change alone suffices to bring about *stimulation of the mucous membrane*, increased peristaltic movements, and evacuation of the bowels. For therapeutic purposes acids can never be conveyed to the intestines directly, because moderate quantities of them, through their rapid absorption, do not penetrate beyond the duodenum. Large quantities, on the other hand, act as caustics.

It is, however, only the *relatively inabsorbable acid organic salts* of the alkalies, *e.g.*, bitartrate of potassium, which get further down in the intestine than do the neutral members of the Glauber's salt group; in this way they render the intestinal contents acid, spur on the peristalsis, and consequently induce *evacuations* in decidedly smaller doses than the neutral salts. Many fruit juices and extracts owe their aperient action to their containing such acid salts. Among these must be specially mentioned the prune and tamarind, as well as the *Triticum repens*.

Very interesting is the *behaviour of the acids in the blood*, and the question as to the *neutralisation of the alkalies* in the latter, and in the organism as a whole.

Since all acids are rapidly absorbed, it was *a priori* believed that after their administration the alkalies of the *blood become neutralised* and carried over into the urine in the form of the corresponding salts. The experiments of Miquel (1851) seemed to support this view, for he showed an increase of the soluble salts in the ash of the urine of dogs to which sulphuric acid had been given; nevertheless, Bence Jones (1849) had observed an increase of acid reaction in the urine after dilute sulphuric acid had been administered; and Eylandt (1855) confirmed this result in regard to inorganic acids and a number of organic ones. That same year (1855) in experiments which Ph. Wilde carried out upon himself, the amount of potash and soda in the urine was not found materially increased after taking sulphuric acid and phosphoric acid. F. Hofmann (1871) fed a pigeon for thirty-nine days with the yolk of an egg, because this yields an acid ash when burned, due to the quantity of lecithin in it. The amount of the ash as a whole, and of the analysed salt, was exactly the same in the urine and excrement, and consequently an abstraction of bases did not occur. Gähtgens (1872) was the first to show that in dogs, after the administration of sulphuric acid, the increase of the fixed bases in the urine is only slight; that therefore an abstraction of them is not attainable in any material degree by giving acids. Finally Salkowski (1875), after giving rabbits sulphuric acid and taurin, which yields sulphuric acid as it is consumed in the body, found fixed bases appearing in increased quantities in the urine.

The behaviour of acids towards the alkalies of the blood can be best understood by the changes which the quantity of *carbonic acid in the blood* undergoes: by giving hydrochloric acid to *rabbits*, it is possible to bring about a fatal abstraction of alkalies without any other coincident effect. Death follows inevitably in consequence of paralysis of the respiratory and vascular nerve centres, so soon as the alkaline reaction of the blood becomes neutral, and the amount of carbonic acid in the latter has sunk to 2·9–2·5 vol. per cent.; but with just as great certainty does immediate restoration of the animal occur, even if it be in the agony of death, as has already been mentioned, if a solution of carbonate of soda be injected into the blood.

NEUTRALISATION OF THE BLOOD BY HYDROCHLORIC ACID AND RECOVERY AFTER CARBONATE OF SODA (RABBIT).
(SCHMIEDEBERG AND WALTHER.)

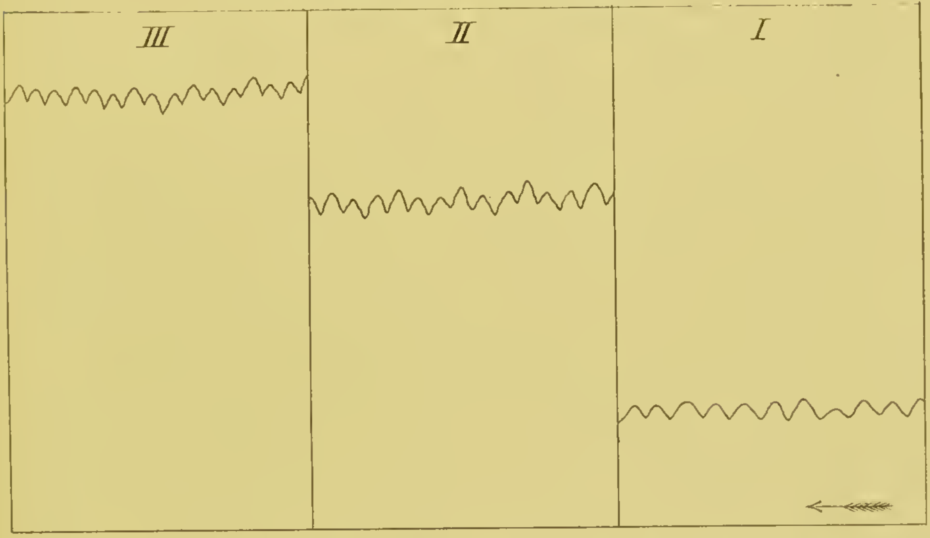


FIG. 7.—Curve showing the effects of hydrochloric acid upon the blood-pressure when administered internally to a rabbit, and the recovery under the injection of carbonate of soda into the blood.

I. Results of the acid. Blood-pressure 28.
II. Four minutes after the injection of carbonate of soda into the blood. Blood-pressure 74.
III. Fourteen minutes later still. Blood-pressure 99.

In dogs a decided neutralisation of the alkali of the blood, after giving acids, never occurs under any circumstances, even when the dose of acid is so great that the animal becomes ill through the caustic effect upon the stomach. Along with the acid, *ammonia* appears in increased quantity in the urine, so that three-fourths of the acid given are secreted, combined with this, and in consequence of this the fixed alkalies of the blood are protected from neutralisation (Walther).

As in the case of dogs, so in the case of human beings, the greater part of the acid taken up appears in the urine united with ammonia (Coranda).

Hence the latter under usual conditions becomes easily and perfectly transformed into urea in the body, this process must undergo an inhibition when acid is given, and perhaps this occurs in the liver, whither the acid goes first of all after its absorption by the portal vein.

In various acute *feverish and chronic affections*, *ammonia* appears *in the urine* in increased quantities (Boussingault, Duchek, Koppe, Hallervorden). How far an increased formation and excretion of acids, or an inhibition of the synthesis of urea is at work from other causes, future investigations will inform us.

Important as is the above described behaviour of the acids towards the fixed bases of the organism, and towards the ammonia in the formation of urea, just as little can a *conclusion* be drawn from these facts *in regard to the influence of these processes upon the total metabolism.* Hence it is for the present impossible to find rational indications for the employment of the acids in sickness. Certain it is that these remedies are of essential importance in *beverages and refreshments* in the treatment of acute feverish diseases. Whether, in addition, a neutralisation of alkalies in the region of the portal vein comes in any way into consideration, is for the present impossible to determine, like many other questions about these regions. Effects in this direction could presumably be produced, not only by inorganic and aromatic acids, but also by pure organic acids of the fatty series, although, as already stated, they become almost totally burned up in the body.

The Mineral Waters.

Being mixtures, these do not belong to any definite pharmacological group, but unite in themselves, more or less perfectly, the *effects of warm and cold water*, of *salts* of every degree of absorbability, of the *alkalies*, and of *carbonic acid*. That the *special constituents* which occur in these waters in infinitesimally small quantities, *e.g.*, iodides, bromides, salts of lithium, and sulphate of lime, do not play any important independent part, need not be again expressly insisted upon in a scientific discussion of them.

The effects of a spring water are consequently only to be judged of according to its chief constituents. To these belong the *water*, the *chloride* of sodium and potassium, the *carbonates* and *sulphates* of sodium, and *carbonic acid*.

The more perfectly these various groups of constituents are contained in water, the more manifold are its actions, and the more numerous the cases in which it promises to be beneficial. Hence the *Carlsbad sprudel* is numbered among the best of mineral waters in existence, although it contains nothing extraordinary, but only the substances above named in a very uniform mixture. This water simultaneously influences the stomach, the intestine, the metabolism, and the secretions of the kidney, in every way at all possible under the circumstances. That the effects of the easily absorbed and of the aperient salts do not interfere with, but can occur alongside of each other, is evident from the fact that Glauber's salt does not affect the absorption and passage of common salt through the organism (Buchheim).

If we keep the commonest laws of Nature in sight, we do not require special proof that the artificially made mineral water has exactly the same importance as a natural one, if both have the same composition, and are taken under the same conditions. This latter demand is by no means so easy to fulfil as would appear, because the complicated conditions which come into question are neither easy to answer nor safe to judge of.

The geography and topography of a watering-place, its height above the sea, the temperature and its oscillations, the moisture of the air, and many other climatic conditions, combine with the actions of the constituents of the spring, and with the nature of the diet and other regimen, to form a sum total of active factors, the importance of which can in general be understood, but in the concrete case cannot be separated, and which cannot in consequence be easily brought about or procured everywhere.

Balneology is consequently a purely *empirical science*, and the object of a high medicinal art. It must, however, grow upon a purely scientific basis, and must free itself more from the dross which still clings to it, partly, though not entirely, as an inheritance from the past. Whoever believes in a difference between artificial and telluric heat, whoever lays stress on the occurrence of infinitesimal traces of certain rare constituents in a spring, or allows even electric currents in them to exert an influence, and in general perceives in mineral waters something other than physical agents, and other than solutions of the substances contained in them,—whoever acts thus deserts not only the field of science, but even that of a pure empiricism, and betakes himself to the realm of faith, and of the medical dogmatism of the vulgar.

3. THE HALOGEN GROUP.

The Chlorine Group.

This group includes the *hypochlorites* as well as the free halogens, *chlorine*, *bromine*, *and iodine.* The few other compounds, *e.g.*, chlorides of phosphorus, are of no practical importance.

The halogens, through the same properties to which they owe their destructive effect upon organic substances in general, cause in the tissues of the living body *caustic actions* of every kind and of every degree, with all the various results and consequences described above.

The immediate alterations of the protoplasm are very much the same as after the corresponding action of acids. Whether the different forms of inflammation, or a perfect destruction (surgical cauterisation) may result, will depend essentially upon the quantity of chlorine, bromine, or iodine, and the duration of the action. Yet iodine cauterises under like conditions far less energetically than either of the other halogens.

The destructive effects of *chlorine* have given it a reputation as an infallible *disinfectant.* As a matter of fact, it is comparatively easy to succeed in destroying those ill-smelling substances round in *putrefying masses*—*e.g.*, sulphuretted hydrogen, sulphide of ammonium—and in imparting to these masses a harmless appearance. We may further assume with certainty that no infectious material escapes its destructive influence, if it can only act in sufficient quantity; but this condition in most cases can only be fulfilled with difficulty, and sometimes not at all. *Chlorine does not act in a specific way as a poison to the protoplasm* of the organism, but destroys it by decomposing or altering the organic substrata.

When, consequently, *infective substances are to be rendered harmless by it*, this can only take place successfully through the destruction of all the media in which they occur, and more or less of all the objects to which they adhere,—as, for instance, the skin and its appendages, or individual parts of other organs, if the object is to destroy the poison of gonorrhœa, of chancres, of corpses, or other infectious substances, as well as when one wishes to free carpets, clothes, and simple objects from infective substances. If the employment of the chlorine is not made in this extensive manner, there is a risk that it may be laid hold of by harmless substances before it has been able to destroy the harmful ones. The *fumigations with chlorine*, so famous in past times, and which were so often ridiculously employed during epidemics, and for the disinfection of the person, have, as a consequence, justly fallen into discredit.

Chlorinated lime is of greater service *for disinfecting*, on a *large scale*, latrines and other centres of putrefaction in which the surroundings do not need to be spared. Still, it is desirable to clean them out first, because the greatest quantity of chlorinated lime which can be employed is not sufficient to disinfect the whole contents of a latrine, even temporarily. In such cases, chlorinated lime is hardly more effective than caustic lime, yet it has the advantage that chlorine gets to those parts of the space to be disinfected which do not come into contact with the caustic lime. The disengagements of the chlorine can be accelerated by dilute crude sulphuric and hydrochloric acid.

Chlorine water, which used in past times to be employed externally as a disinfectant and caustic, and internally in infectious diseases, has now rightly become obsolete. *Chlorine* cannot possibly have any *action after its absorption*, because the small quantities employed medicinally are fixed in the contents of the stomach by the albumens and other substances, and consequently cannot in the free state reach the blood, to say nothing of the urine, as is irrationally asserted at times.

The *compounds of iodine with the albuminous substances* are very unstable, and are consequently decomposed by dialysis, and by coagulation of the albumen (Berg and Böhm).

If the *skin* is painted with a solution of iodine, the epidermis assumes either a yellow or a more or less deep brown tint, according to the quantity of the iodine deposited there. In consequence of the *irritation* which the remedy causes, *inflammation running a chronic course* results at the point of application, or there may only be an increase of the usual nutritive processes, under the influence of which, as already mentioned in a general way, *pathological products are frequently absorbed.*

The importance and *preference* which iodine can claim *before other stimulants* of this kind consist in the fact that it remains a long time adherent to the point of application, and that the action penetrates thence to a certain depth because of the volatility of the substance, and also in the fact that after a little experience we have in our hands the power to impart any desired degree of stimulation by a repeated application of greater or less quantities of the remedy, as well as to keep this up for a considerable time in a very equable degree. To these conditions, and not to any specific actions, must we refer the cures which are often achieved more quickly and more certainly than with other stimulants, by treating exudations and hypertrophies with so-called "*painting with iodine.*" Experience teaches how the action must be regulated in each case, both as regards strength and duration, in order to guarantee the most favourable result.

The internal employment of iodine as a local remedy for the habitual vomiting of pregnant women, in sea sickness, and in similar conditions, or in place of iodide of potassium in syphilis, has at present been almost given up. On the other hand, it is used in the form of solutions (tincture of iodine and liquor iodi) as a caustic, in order to *bring about a so-called "adhesive" inflammation,* to effect the union of the inner walls of ovarian cysts and hydroceles after they have been evacuated. Even in this case iodine offers the advantage that it adheres for a long time, and consequently keeps up a curative inflammation for the necessary period without causing the formation of an eschar through its uniting with the tissue-forming substances.

In some cases after the injection of such solutions of iodine into the ovarian cysts previously tapped, *symptoms of poisoning* have occurred, consisting in drowsiness, in pains in the region of the stomach, and violent vomiting. The masses vomited contained the peeled-off gastric glands, and at first free iodine, and subsequently combined iodine in great quantities (E. Rose).

In *dogs*, after the injection of fatal doses of iodide of sodium, and of iodine dissolved in iodide of sodium, only renal hæmorrhage, but no alterations of the mucous membrane of the stomach, could be found (Böhm); while the latter, *in rabbits*, after subcutaneous application of this drug, was found swollen, hyperæmic, and ecchymosed (Binz). In these cases of poisoning, iodine probably passed through the organism as iodide or albuminate, and then became excreted into the stomach in the form of hydriodic acid, analogous to hydrochloric acid, and became decomposed under the appearance of free iodine.

Among the symptoms in human beings, Rose observed the *disappearance of the arterial pulse*, as well as paleness and coldness of the skin, while the heart's action was more energetic. He attributes these appearances to a contraction of the lumen of the vessels. Yet in animals, after injection of double iodide of sodium, no rise of blood-pressure occurs: this points to such an alteration in the diameter of the vessels.

Dogs in which iodine dissolved in iodide of sodium was injected into the blood (40 mg. to every kg. of body weight), died with the same symptoms, and in the same time as after an injection of iodide of sodium (Böhm). Yet it is not permissible to conclude that in both cases it is a question of the action of iodine.

4. THE GROUP OF OXIDISING AGENTS.

(*Oxygen Group.*)

The physiological oxidations in the organism are caused entirely by the oxygen of the blood. The ordinary *oxidising agents* act only at the point of application. They evoke various forms and degrees of *caustic action and destruction*, and are practically employed for this purpose.

Permanganate of potash is an energetic *disinfectant*, which answers especially for the destruction of ill-smelling harmful products of decomposition in the uninjured skin, in wounds, ulcers, and easily accessible cavities of the body. Since it, however, becomes rapidly and totally decomposed by small quantities of numerous organic substances, oxidising them, the *disinfectant action* remains limited to the merely *superficial parts*, or else it affects only those substances which are readily oxidisable, but not at the same time injurious. Consequently the remedy can only be employed with advantage for freeing the external skin from adherent infectious material, and beyond this for *washing out the mouth.* Along with this, it is to be remembered that the portions of skin in question become temporarily coloured brown by the peroxide of manganese which is precipitated.

The *caustic action* which permanganate of potash causes, remains *limited to the superficial layers of* tissues, upon the same ground as the disinfection does. As a caustic for medical purposes, it is moreover not adapted, because at ordinary temperatures it only slightly attacks albumens.

For disinfection on a large scale this remedy can be but little used, because of its price.

Chromic acid, which is known in the solid state only as the anhydrate (CrO_3) can hardly be classed pharmacologically among oxidising agents, because in it the *acid action* predominates. It is used on a limited scale as a *caustic in surgery.* It is very difficult, however, to restrict the extent and depth of the caustic action, because the acid is deliquescent, and does not form a firm eschar which protects the neighbouring parts.

The *acid chromates* are weak caustics. In the form of these salts, chromic acid, which, according to results on animals, is absorbed even from the surfaces of wounds, is excreted by the kidneys, thus causing parenchymatous nephritis (Gergens).

To the strongest oxidising agents belongs the triatomic oxygen or *ozone*, which likewise only acts locally: when inhaled it causes violent irritation of the respiratory tracts (Asmuth and Al. Schmidt). It occurs in large quantities in *oil of turpentine* which has stood a long time in the air, and is used in this form in poisoning with phosphorus, for the purpose of oxidising the latter in the stomach. The phosphorous acid which thus results forms a crystallisable compound with the oil of turpentine. The utility of this remedy is still doubtful. If the turpentine oil contains but little ozone, and if the oxidation of the phosphorus does not result rapidly, the absorption of the latter may be favoured in consequence of its being dissolved by the turpentine.

Peroxide of hydrogen (H_2O_2) acts only upon easily oxidisable compounds. It is decomposed (catalysed) by fresh blood in water and ordinary oxygen (O_2), without the constituents of the blood becoming oxidised. The lymph of small-pox, gonorrhœal secretion, and the products of other sores are said to act in the same way when they contain infectious material (Schoenbein). Consequently, peroxide of hydrogen has been recommended in such cases *as a disinfectant*, but we must not assume that the infectious substances become themselves destroyed, even if they do.

Sulphurous anhydride (SO_2), which is formed when sulphur is burned, is not an *oxidising agent*, but, on the contrary, a powerful *reducing agent*, yet it may be discussed here. Its destructive action upon colouring matters, and its use as a bleaching agent, depend upon the abstraction of oxygen. From a pharmacological point of view, its *acid action* and special properties, to which this compound owes its great poisonous action upon all living animal and vegetable substances and their germs, come, moreover, into consideration. The sulphurous acid remains much longer than chlorine in organic mixtures, for chlorine unites very rapidly with all possible substances, consequently it is more efficient for the destruction of the *causes of fermentation and putrefaction and disease than chlorine.* It is certain that no remedy can replace it in the disinfection of *dwellings and other rooms.* For this purpose 15 g. of sulphur must be burned to every cubic metre (= 24 grs. for every cubic yard of space) (Hoppe-Seyler), and the room is kept closed for some hours. After this it is well to pour out a small quantity of ammonia in the room, in order to neutralise the sulphuric acid which has formed, and which adheres to everything present.

CHAPTER V.

THE COMPOUNDS OF THE HEAVY METALS AND ALUMINIUM AS NERVE POISONS, MUSCLE POISONS, AND ESCHAROTICS.

Of the compounds of the heavy metals, only those need be considered here in which the *metal is combined with oxygen*, or in which the former readily gets to the latter by a process of double decomposition, as, for example, in the case of the halogen salts. The effect after absorption does not depend upon the entire molecule of the compound, but upon the *metallic oxide*, which exists, as it were, dissolved in the organism.

The *organic compounds of the metals*, on the other hand, in which the metal is united with the carbon, do not fall under this head, because they do not owe their action to the metal specially, but to the construction of the whole molecule: it is only when this is perfectly decomposed, and the metal passes into the oxidised state, that the typical metallic action shows itself. For example, the salts of lead-triethyl, and of kakodyl oxide act in this respect like other bases of the fatty series; it is only when they are decomposed, and when the lead or arsenic appears in the body in the "oxidised" state, that the typical effects of these metals show themselves.

The pharmacological relationship of the heavy metals to each other is mainly determined by their chemical relationship to the albuminous bodies, which, under certain conditions, unite with the metallic oxides to form albuminates. The latter are also formed in the living organism, that is to say, at the point of application, which is thus subjected to changes which have the same fundamental character in the case of all the metals. On the other hand, the actions upon the nerves and muscles, which occur after absorption, are more or less characteristic of each metal, and consequently cannot be considered as due to its general reactions with albuminous substances. The latter merely bring about the solution of the metallic oxides in the alkaline fluids of the body, but even this does not necessarily occur in all cases. In this state the metal exerts its specific molecular influence upon the *nerves* and *muscles*, and we may also say upon the *seats of the metabolic processes.*

Consequently the metals belong to the nerve and muscle poisons as regards this trait of their pharmacological behaviour. We can *more or less entirely exclude their local effects*, if, to start with, we employ those preparations in which the metal is already suitably combined with albumen, or with other organic substances. In this form absorption of the salt follows without the place of its application having to provide material for the formation of these absorbable compounds; consequently it remains unaltered.

In accordance with the foregoing explanations, it is necessary to *distinguish the local from the general actions of the metals.* The former can be treated of in one group, because of their similarity in character and origin, while as regards the general actions, almost every metal forms a special pharmacological group.

1. THE LOCAL ACTIONS OF THE SALTS OF THE HEAVY METALS AND OF ALUMINA.

Albuminous substances combine with the metallic oxides as with other bases to form peculiar *albuminates*, which are insoluble in water. If a simple metallic salt meets with albumen in neutral solutions, a precipitate is formed consisting of albumen of the metallic oxide and of the acid present. The latter in most cases can be readily washed out of the precipitate by means of water; it is therefore, so to speak, set free, and can consequently act independently upon the albumen.

While it was at one time impossible to obtain *metallic albuminates* of constant composition, stable compounds of albumen, with oxide of copper and free of acid, have latterly been made; they contain both components in multiple yet fixed proportions (Harnack).

The same process follows *when the metallic salts meet with the tissues of the living organism*, as when they act upon the solutions of albumen. The albuminous and connective substances unite with the metallic oxide while the acid of the salt employed brings about alterations of the tissues independently, just as when it is employed in the free state to start with. In consequence of these processes there results *a caustic action*, which is dependent partly upon the influence of the metallic oxide, and partly upon that of the acid.

The intensity and character of the caustic action are determined on the one hand by the nature of the resulting metallic albuminate, and on the other by the quantity and properties of the *acid* which participates in the process. If the latter in itself be but little caustic, and if it occur in relatively small amount in a basic salt whose *metallic oxide* forms with the nitrogenous constituents of the tissues an insoluble firm mass which cleaves closely to the subjacent portions of the body, the *eschar* (p. 133) prevents the further penetration of the remedy, and the cauterisation remains limited to the superficial parts. The *inflammatory irritation* in such cases soon passes off, because the acid is absorbed or simply washed away, while the eschar remains fixed to the spot, and causes effects which receive the name of an *astringent action*, or, for brevity, *astringency*, and which are taken advantage of extensively for therapeutic purposes.

The *essence of astringency* consists, from a practical point of view, in the reduction of the intensity of those processes which are found in inflammation. It lessens or removes the swelling and luxuriancy of the cellular elements of the tissues, suppresses immoderate secretion of mucus, and restrains the formation of exudations and pus.

All substances can *act astringently* which form with the albuminous and the gluten-yielding tissues firm *combinations which are insoluble in water*, and in the watery fluids of the organs. At all events, the astringent action is dependent upon the occurrence of the above combinations on the surface of the tissues, in the inter-cellular substance and the inter-cellular fluid. Yet these processes which are there at work cannot be more distinctly defined. Since there is reason to believe that in inflammation there is a porosity and too great permeability of the tissues, then the astringency may be considered as the counterpart, *i.e.*, shrinkage of them.

In all probability this is really the case. Its occurrence we must imagine as taking place in the following way :—The cellular elements of the organs, as well as the walls and orifices of the various nutritive canals, the lymph channels, the stomata, lymph spaces, capillary blood-vessels, and capillary lymphatics become covered with a thin layer of these compounds, but only to the extent that the morbidly increased separation and accumulation of nutritive material is lessened, while the normal nutrition is not prevented.

This change in the tissues is *always at first accompanied by inflammatory irritation*, even when the liberation of acid from the metallic salts does not co-operate. For it is still a case of a *caustic action*, which only differs from the ordinary one as regards its consequences. Hence all astringents, even the various forms of tannic acid, which, least of all, show collateral actions, arouse acute and chronic inflammation if they be employed in large quantities, or for a long time.

Since, moreover, the alteration which is at the bottom of the astringency prevents the deep penetration of the substances employed, the curative effect as a rule only appears with certainty in those cases where the *seat of the affection is superficial;* parts more deeply situated are, at the utmost, only indirectly affected. Hence the *chronic catarrhs of the mucous membranes* form the special realm in which the astringents have their highest therapeutic value.

As regards *the salts of the heavy metals* in particular, some *act almost solely as astringents*, provided they are not employed in immoderate quantities. To these belong most notably *basic acetate of lead* in which the acetic acid as a caustic constituent comes only slightly into consideration, while the firm, almost insoluble, compounds formed by the oxide of lead with the albuminous substance bring about a very high degree of shrinkage of the tissues.

In contrast with the astringent metallic salts stand the *more or less purely caustic* ones. If the metallic oxide has a great inclination to unite with the nitrogenous constituents of the tissues, but the resulting products, especially the albuminates, be of a loose structure, and the morphological elements are at the same time so far destroyed that they lose all connection with each other, and if, finally, a secretion of fluid exudation is associated with all this in consequence of a strong inflammatory irritation, then the *eschar consists of a soft* pultaceous mass, which is easily shed, and consequently forms no hindrance to the deeper penetration of the metallic salt. The caustic action is in this case intense, even when the action of an acid does not specially come into consideration.

Mercuric oxide answers these claims most perfectly, for it forms a soft, only slightly adhering eschar, and can, not only in the form of its salts, but also directly of itself, unite with the albumen. Consequently its salts do not act as astringents, if we except the white precipitate.

All *the other more important metallic oxides*, if we leave the acid action of their salts out of consideration, take *an intermediate position between lead* and *mercury.* Yet it is scarcely possible to arrange them in a series with any approximate certainty; for in most cases, it is utterly impossible to have a purely metallic oxide action without getting the simultaneous caustic action due to an acid, because the oxides do not unite directly with the albumen, and because they thus often do not form any salts in which the acid does not play an essential part in the caustic action. *Usually, indeed, the acid is the main item therein.* The strength of the caustic action of the metallic salts depends upon the properties and solubility of the latter.

At the head of the list in this connection stand the *metallic chlorides.* Whenever one of the chlorides is soluble in water, it of all the normal salts of the same metal is the most caustic. As regards this, we need only refer to the chlorides of mercury, zinc, and iron, as compared with the other salts of these metals. In the case of the chlorides there is not only the action of hydrochloric acid, but it seems also that free chlorine comes into action, for Bryk found chlorinated organic compounds in the eschars after the use of chloride of zinc. In this case we would have to do on a small scale with a similar process to that which occurs in the chlorination of organic substances under the influence of pentachloride of phosphorus.

The metallic chlorides, which are little if at all soluble in water—as, for example, *the chlorides of silver and lead and mercurous chloride*—behave, on the other hand, almost indifferently. For the same reason the *bromides* and *iodides* are almost inactive. Yet in the case of the latter—as, for example, ferrous iodide—the iodine may be set free at the point of application, and so cause a caustic action.

The *mercuric iodide* is a very decided caustic in spite of its insolubility in water, because it acts towards albumen just as the oxide does (p. 161).

Next to the chlorides, as regards strength of caustic action, come the *nitrates.* Since the *nitrate of silver* is easily soluble in water, while chloride of silver, on the other hand, is not, the former is the most energetic salt of this metal. A like position is taken by *nitrate of lead* among the lead salts. With respect to the *nitrates of mercury*, another circumstance has to be considered, viz., that they readily give off nitric acid, and thus form basic salts; consequently, though they are no less caustic than the bichloride, the alteration is limited more to the surface because the co-operating nitric acid coagulates the albumen, and thus impedes the further penetration of the remedy.

Next to the nitrates in the order of sequence of the caustic metallic salts come the *sulphates*. The sulphate of zinc, for example, is considerably less caustic than the chloride of this metal.

In the case of the *organic salts* it is essentially *the metal* which *determines* the intensity and nature of the effect. The behaviour of the individual metals in this direction can be best seen in the acetates. As regards the acetates of lead and mercury, we may refer to what has been already said (p. 161).

In accordance with this, the former is an astringent, the latter a caustic. Next to lead comes iron, and then follow, in no sharply definable series, *zinc*, *copper*, *silver*, and *tin*. These all, however, stand nearer to lead than mercury.

The *therapeutic importance of the simple metallic salts* is to be sought, not only in the fact that through some various degrees of caustic action may be caused, and through others a weaker or stronger astringent action; but it specially depends upon the fact that we can combine the actions, so that even when only one preparation is employed, a more or less astringent action may follow a preceding caustic one, which evokes inflammation or destruction of the tissues. Among all the metallic salts, *nitrate of silver* takes the leading position as regards this combined action. It causes first of all an intense destruction, which remains limited to the most superficial layers of the tissues, for reasons above given (pp. 160 and 161). Then presently there comes into play the astringency, which is, to some extent, dependent upon the firm adhesion of the eschar.

The *indications for the employment of nitrate of silver* follow directly from this behaviour on its part. The remedy is always suitable for those cases where the tissues are already so far altered in superficial chronic inflammations that their restoration seems to be no longer possible. Here the indication is to remove the morbid parts by destroying them, and either to encourage the nutritive processes in other parts by the stimulant, or to moderate them by the astringent action.

Combined effects, similar to those caused by the nitrate of silver, can be induced by other metallic salts. For practical purposes, the *sulphates of copper and zinc* are the most frequently used. In these the astringent action keeps in the background, as compared with the caustic action, which mainly induces an inflammatory irritation, and this probably because a firmly adhering dry eschar is not formed by the caustic.

As regards their therapeutic significance, we may classify *in three groups the metallic preparations* in use as local remedies. The first of these comprises *the pure caustics*, the second those *preparations which are at the same time caustic and astringent*, and the third group the *metallic astringents*, including the salts of alumina. This classification, however, is only of general value, since the nature of the local action is dependent not only upon the preparation employed, but also upon many other circumstances. To these belong the quantity of the remedy, the concentration of its solutions, the nature of the place of application, the length of time it is acting, and the manner and means of its employment. For example, an excess of the caustic and some of the acid may readily be got rid of by washing them off with water, or with a weakly alkaline fluid, by means of a painter's brush. Thus, the caustic action can be moderated to any desired degree as compared with the astringent one.

Some metallic compounds find the conditions for their action only at those places where *free acids* occur—such as, more particularly, in the stomach and in the cutaneous glands. In the form of the double salt, *tartar emetic* has hardly any caustic action, but in the localities mentioned it is decomposed by the acid and transformed into a simple caustic compound of antimony. So, too, in the skin; instead of diffused inflammation occurring there, pustules, arising from the follicles, are developed. If we employ *sulph-antimoniate of sodium*, or Schlippe's salt ($Na_3SbS_4+9H_2O$), instead of tartar emetic, the tips of the pustules are coloured red because this salt becomes decomposed by acids with separation of penta-sulphide of antimony (Buchheim and Zimmermann).

The *basic nitrate of bismuth is* insoluble in water, and is consequently under ordinary circumstances inert. It may even be brought into the stomach in large quantities without doing harm, yet a small quantity becomes dissolved *in the acid fluid there, and then acts as an astringent.* Since its solution—that is, its transformation into the active compound—is limited by the dilute state of the acid of the stomach, this preparation can be employed with advantage in those cases in which it is important *to keep up an uniform mild degree of this action for a long time*, that is, for weeks, or even for months. It is only when there is much acid in the stomach that it can have a caustic action (Bricka).

As *pure caustics* we may instance *corrosive sublimate, red and yellow mercuric oxide, mercuric iodide, chloride of zinc, tartar emetic, mercurous nitrate, terchloride of antimony* (*butter of antimony*), *chloride of zinc, &c.* The *caustic action, as well as astringent action*, is caused by the *sulphates* and *chlorides of iron, sulphate of copper, sulphate of zinc, acetate of zinc, nitrate of silver, iodide of lead, lapis divinus* (*sulphate of copper, alum, and nitre*), *the normal and the basic acetate of copper, nitrate of lead, sulphovinate of lead, &c.;* of substances which are *mainly astringents*, there are *potash-alum, neutral and basic acetate of lead, oleate of zinc* (i.e., *zinc oxide as it occurs in ointments*), *basic nitrate of bismuth, white precipitate, &c.*

The cheap *metallic salts*, especially crude ferrous sulphate, are employed also as *disinfectants*. By means of them many ill smells due to decomposing substances may be got rid of; more particularly the sulphuretted hydrogen unites with the metal of the salt employed, and the ammonia with its acid. A sufficiently destructive action of the metallic salts upon the lower organisms is only to be expected where they are made use of in large quantities. These substances have consequently no special advantages over caustic lime.

2. THE ACTIONS OF THE METALS AFTER THEIR ABSORPTION INTO THE BLOOD.

We have already (p. 159) indicated *the form in which the metals become absorbed.* All of their combinations which are soluble in alkaline albuminous fluids can make their way into the blood, because they are not fixed at the point of application. Yet the transit of these substances only takes place as a rule very slowly, because of their colloid nature. Since the acids of arsenic are readily soluble, both in the free state and in the form of salts, and do not form any albuminates, no obstruction stands in the way of their rapid distribution through the body.

It is the *absorption of the metals from the stomach and intestine* which takes place with the greatest difficulty. Some of them when given internally are hardly taken up at all in the blood; others are taken up, yet so slightly, that when given thus they produce no appreciable general effects, even when the administration is kept up for a considerable time.

Among these metals are manganese, iron, cobalt, nickel, cerium, copper, zinc, silver, and tin.

In the case of dogs, even after taking the double salts of manganese for months by the mouth, only doubtful traces of the metal can be obtained, even when great quantities of the urine have been collected; yet it very readily makes its way through the kidneys when administered subcutaneously (Kobert). The behaviour of iron and nickel is similar.

It is only when from the outset the metallic compounds are brought in considerable doses into the stomach, and cause an acute catarrh of the digestive tract, that the metal appears in large quantities in the urine. On the other hand, this does not occur if such doses are gradually reached by the continued administration of increasing quantities. The catarrh also of the stomach is absent in these cases.

Here we have evidently to do with a gradually supervening reduction of the susceptibility of the mucous membrane to the caustic action.

These conditions have not as yet been sufficiently regarded; consequently it is hard to decide how far the absorption took place from the intact mucous membrane in those cases where *metal appeared in the urine in large amounts* after internal administration. Feltz and Ritter found a great amount of copper in the urine, when they caused gastro-enteritis in dogs by means of the sulphate or acetate of this metal. Here there can be no doubt as to the connection between the absorption and the morbid state of the mucous membrane.

Besides arsenic, *mercury* and *lead* are the only metals *which cause general effects when administered internally*. *Mercury* is absorbed in so large a quantity, even in many cases where its insoluble compounds are employed, that the signs of poisoning appear even in a few days, and the metal is to be found in the organs as well as in the urine. *Lead* produces its characteristic action less readily. It is usually after weeks and months of the administration of its compounds that these symptoms come on which are designated as chronic lead poisoning. Those effects of this metal which are not due to a local caustic action, cannot be induced quickly by means of its salts, no matter how they may be administered.

Although in the case of human beings urine contains antimony even when the pentasulphide is taken (Solon, Schäfer), yet cases of poisoning with antimony without symptoms of gastro-enteritis are unknown.

The *elimination of the metals* from the organism takes place in the form of their double compounds with albumen or other organic substances, and it occurs *mainly through the urine*, partly, however, *with the bile*, for the metal can be found in the latter, and in the fæces even after subcutaneous injection. The view that the intestinal mucous membrane shares in the excretion, apparently disproved in the case of iron (Quincke), has recently been confirmed in the case of manganese by direct experiment (J. Cahn).

In their passage into the urine all metals without exception cause *disorders of the kidneys;* these consist in the epithelium of the convoluted and straight *tubules* taking up the metal and then gradually breaking down, and being partly thrown off as epithelial casts; the tubules are thus laid bare. The *glomeruli* remain at first intact, and afterwards succumb to analogous changes.

Similar real inflammations are brought about by numerous caustic and irritant substances as they are excreted in the urine.

1. *Arsenic.*

The effects of arsenic depend upon its oxygen compounds, *i.e.*, *arsenious acid and arsenic acid.*

Kakodylic oxide and *kakodylic acid*, in both of which arsenic is combined with carbon, act in the unchanged condition in a way of their own (C. Schmidt and Chomse). Yet, like other organic compounds of the metals, they probably decompose gradually in the body, appearing in the form of one of the above degrees of oxidation, and they then evoke the action of arsenic (Lebahn, Schulz).

Both of the acids of arsenic cause in man and mammals violent *symptoms in the stomach and intestine*, exactly resembling an acute gastro-enteritis; these have therefore been considered in past times as due to a direct caustic action upon the intestinal mucous membrane.

Arsenious acid, which is usually the prime factor in these cases of poisoning, is in fact *a caustic*, and is still used as such in surgery, and more particularly in dentistry; but the caustic effect, which is possibly due merely to its acid action, only takes place very slowly, no matter where it be applied. The rapid occurrence of symptoms in the stomach and intestine do not harmonise with this. They are rather to be *attributed* to the intense *disturbances of the circulation*, caused by the arsenic, and these consist in a *very great depression of* *the arterial blood-pressure*, which sinks at last so low, that there is no longer sufficiency of the circulation (Böhm and Unterberger).

The cause of this lowering of the blood-pressure has not yet been fully cleared up. The vessels of the abdominal organs certainly participate in this in a prominent and probably peculiar manner. They lose their tonus, without their nerves of supply sacrificing their irritability; for reflex stimulation and direct stimulation of the cervical region of the cord raise the blood-pressure again, even when artificial suffocation has lost its power to do so (Boehm and Pistorius).

It is at last impossible by this means, or by *direct irritation of the splanchnic*, to attain a rise of arterial pressure; though, strikingly enough, irritation of the sympathetic in the neck maintains its action upon the vessels of the ear of the rabbit in every stage of arsenical poisoning (Boehm and Unterberger).

In addition to dilatation of the vessels, arsenic causes also *cardiac paralysis* (Brodie, Blake, Sklarek, and Cunze), and that in the same way as prussic acid and emetine do; this is especially well seen in frogs.

In mammals the paralysis of the heart becomes really prominent only when large doses of arsenic are taken rapidly into the blood: but even in far advanced poisoning, and after the blood-pressure is very low, the heart continues still to work with sufficient force to keep up a very fair blood-pressure when the aorta is compressed (Boehm and Unterberger).

Very grave changes in the mucous membrane of the intestinal canal underlie those symptoms in the stomach and intestine, which chiefly contribute to form the picture of acute arsenical poisoning, and which consist in vomiting, pains in the abdomen, and diarrhœa with simple and bloody stools. This is mainly due to hyperæmia and extravasation into the mucous membrane, and to degeneration and detachment of the intestinal epithelium (Boehm and Pistorius).

In man there are usually hyperæmias, hæmorrhages, and ecchymoses, swelling of Peyer's patches, and of the solitary glands, exudations and ulcerations of the mucous membrane.

In dogs and cats, the mucous surface of the intestine is covered with false membranes, composed of intestinal epithelium, which has undergone fatty degeneration, or transformed into hyaline balls, or drawn out into tubes; and also of round cells and masses of detritus. After removal of these overlying masses, the surface of the mucous membrane is seen to be coloured a deep purple red, in consequence of a high degree of hyperæmia of the capillaries of the villi.

One can hardly doubt that *these alterations of the intestinal mucous membrane are due to dilatation of the vessels.* It may be taken for granted that the hyperæmia of the capillaries of the villi induces the transudation of a coagulable fluid, which loosens the epithelium of the villi, and as it coagulates forms with it the false membranes (Boehm and Pistorius).

Ordinary arsenical poison *runs its course* with the most violent symptoms connected with the stomach and intestines. In cases where the poisoning in human beings *progresses* very rapidly, death at times comes on with *coma*, *delirium*, and *eclamptic attacks*, without corresponding symptoms and pathological appearances, pointing to an affection of the intestinal canal. In such cases the disturbance of the circulation dependent upon the great reduction of the blood-pressure, is to be looked upon as the immediate cause of death. The insufficiency of the circulation causes the suppression of the functions of the brain and medulla oblongata so rapidly that the intestinal symptoms have no time to develop, although in animals even forty minutes suffice, after injection of the poison into the blood, to bring these symptoms to their full height.

A *direct action of arsenic upon the central nervous system* of human beings and mammals, seems to come into question only in those protracted cases of poisoning in which the symptoms of paralysis have a certain character of their own.

The *chronic form of arsenical poisoning* which develops under the long-continued action of oft-repeated small quantities of the poison is characterised by the occurrence of manifold disturbances of nutrition. In addition to the symptoms in the stomach and intestine, there is catarrh of the throat and conjunctiva.

Amongst the nutritive disturbances, *fatty degeneration* of the liver, spleen, cardiac muscle, and kidneys, plays a prominent part; in the case of the latter, the above described form of *nephritis* (p. 167) shows itself in animals. *The skin with its appendages* is *considerably affected*; it takes on a cachectic tint, becomes dry, and there develop on it eruptions and ulcerations which have been ascribed to the local effect of arsenical dust, because they occur in smelters. Yet these alterations, as well as the falling out of the hair, and occasionally also of the nails, have possibly a similar origin to that of the intestinal symptoms.

The *cerebral signs of chronic arsenical poisoning* consist in mental depression, headache, neuralgias, and in motor and sensory disturbances of various kinds. As to the origin of these, no positive statement can safely be made. Probably they result not only from the general nutritional disturbances, but depend upon a direct influence of the arsenic *on the nutrition* of the respective organs. The disappearance of glycogen from the liver of animals (Salkowsky), must be judged of similarly.

In contrast to these deleterious effects from chronic arsenical poisoning stand those effects of the metal which, under special conditions, *favourably influence in a certain direction the nutritive condition of the organism.* In connection with this, the accounts which have been given as to the arsenic eaters in Styria are very interesting. In that country the men, and occasionally the women, are in the habit of taking from an early age gradually increasing doses of arsenic, with the intention of keeping them healthy and strong, and of inuring themselves to the exertions of mountain climbing. In some cases the dose taken at one time amounted to 0·3–0·4 g. (5–6 grains) (Knappe and Schaefer). In those districts arsenic is also given to the domestic animals with their food for the same purpose. Horses are said to get a more glossy appearance, and greater roundness of form.

Since the beginning of this century many investigations have been made as to the effect of small doses of arsenic upon men and animals; yet the accounts refer mainly to the state of the respiration and pulse as regards frequency, and also to the nature of the heart's action, the muscular energy, the appetite, and so on. The experiments, hitherto, would be that in general all functions, even those of the glands, undergo an increase.

More exact experimental investigations have proved that after taking arsenic there is an increased *deposition of fat* (Roussin, Gies), and in young rabbits and pigs a considerable *increase in the longitudinal and transverse growth of the bones;* along with diminution of the corpuscles of the bone, decrease in the size of the *Haversian* canals, and increase of the compact part of the osseous substance (Gies).

The injurious as well as the beneficial results of the use of arsenic point to *alterations in the metabolic processes.* According to investigations up to the present time, it is impossible to decide with perfect certainty in what these essentially consist.

In fowls and pigeons, C. Schmidt and Stürzwage found a *decrease in the elimination of carbonic acid*, and in cats a simultaneous *reduction in the quantity of urea.* With respect to the latter, the experiments on man and dogs (Lolliot) and on sheep (Weiske) gave the same results as regards urea. In chronic poisoning, caused intentionally in man, the urea was lessened, but the uric acid increased (Ritter and Vaudrey).

In the case of a dog in nitrogenous equilibrium no increase in the excretion of urea occurred (Fokker). On a fasting dog small non-poisonous doses of arsenious acid produced *no noticeable effect upon the metabolism of albumen* (v. Boeck). Somewhat larger doses of arseniate of sodium, amounting even to 10 mg. per kg.

($\frac{1}{12}$ grain per lb.) of the weight of the body, caused, on the other hand, in fasting dogs, an *increased excretion of nitrogen by the urine* (Gaehtgens and Kossel). Along with this the latter continually sinks while the food is withheld, *i.e.*, the increased breaking up of the albumen becomes again lessened as the administration of arsenic ceases, which is a proof that this change in the metabolism is really an effect of the arsenic (Gaehtgens).

The *temperature of the body* was found below the normal in man and animals (Vaudrey, Cunze, Lolliot).

When we glance over the results of these investigations we meet the same *contradictions as* is the case in the influence of many other agents upon metabolism (quinine, p. 82, alkalies, p. 135). Consequently, even in this case, we cannot help thinking that arsenic influences the metabolic processes from different directions in conflicting ways, and in this it may be a matter on the one hand of the results of the vascular *dilatation* already described, and on the other hand of a direct influence of the poison upon the elements of the tissue where the metabolic processes occur. But here begins the realm of speculation, for it is neither possible to make any definite statement about the behaviour of arsenic at the seats of metabolism, nor to determine the influence of vascular dilatation upon the nutritive processes in each of the tissues and organs. In the meantime, there is merely a certain degree of probability that the increased decomposition of albumen depends on one or other of these factors. On the other hand, it may be assumed that the congestion of the digestive canal, even though it does not lead to severe affections of the mucous membrane, causes functional disturbances of these organs, and gives rise to obstruction to the digestion and absorption of the food, so that the material for the metabolism is reduced, and the excretion of nitrogen and carbonic acid lowered.

Since, consequently, the nature of the *action of arsenic* is still very much shrouded in darkness, *a rational indication for its employment* therapeutically is not at present to be thought of. Even the empirical grounds for the latter are very uncertain. Besides the "*diathetic*" *conditions* in which arsenic is at times employed with the same idea as iodide of potassium, there are some *cutaneous affections*, especially psoriasis, and certain cases of *intermittent fever*, as well as *neuralgias and neuroses*, which we occasionally attempt to subdue with this remedy. Even after a careful sifting of statements, there remain cases of these diseases in which a beneficial effect of the remedy is not to be denied. The results would be presumably more constant if the arsenical compounds could be used in sufficient quantity a longer time without injuring the stomach or intestinal canal, and without evoking general symptoms of poisoning.

Even as regards the explanation of these curative effects, we are thrown back upon possibilities and probabilities. We can, in general, however, assume that *the curative results are dependent upon metabolic changes and alterations of the nutritive processes*, which in many cases probably affect only individual organic areas. In the last respect it seems not improbable that the vessels of the skin experience dilatation in a manner similar to that in the intestine, though in a far less degree, and that in consequence of the supply of blood being increased, but not so strikingly so as to be seen from the outside, the nutrition of this organ is influenced at one time in a favourable manner, at another time, as in chronic poisoning, in an unfavourable manner.

When *arsenic* is compared with quinine *as a remedy for intermittent fever*, certain negatively interesting aspects present themselves. The compounds of arsenic are not antiseptics in the same sense as quinine. Arsenious acid does not suppress the putrefactive processes properly so called, but is merely a preservative agent, because it kills insects and worms with facility. An analogy between arsenic and quinine is to be found in the fact that the latter in small doses raises the temperature of the body, and in this case, like arsenic, accelerates metabolism. Nevertheless, it is evidently only a matter of similar results due to totally different actions; moreover, arsenic is anything but a febrifuge remedy. If, however, it cures intermittent fever, this fact confirms the conclusion deduced in the case of quinine, that the efficiency of a medicine in this disease has no connection with its general febrifuge properties.

2. *Antimony.*

The *effects of antimony* which are produced in animals after the injection of the double salts, *e.g.*, of tartar emetic, into the blood or under the skin, *almost exactly resemble those of arsenic;* even the increased disintegration of albumen in fasting dogs is to be seen (Gaehtgens).

The blood-pressure in the arteries falls in a slight degree, because the vessels become dilated, and at the same time stimulation of their nerves gradually loses its effect; yet the heart continues to work on powerfully, so that through compression of the aorta, and by means of digitalin, considerable pressure can *still be brought* about in the arteries.

When the course of the poisoning is rapid, death in convulsions supervenes in consequence of the disturbance of the circulation. In *dogs* vomiting and violent intestinal symptoms with bloody stools come on. In *frogs*, first of all, the heart is paralysed, the motor nerve mechanism first, and then the cardiac muscle; simultaneously with this the functions of the central nervous system cease. Upon the voluntary muscles antimony acts only as a depressant.

The *difference between the effects of the two metals* only shows itself distinctly when the compounds of antimony are administered by the mouth. They then cause in small doses merely vomiting, and in large doses a local caustic action. This is wanting when preparations of arsenic are used, and the vomiting is blended with the rapidly supervening intestinal symptoms.

The cause for this very essential difference in the comportment of the two metals is entirely to be found in the fact that the *compounds of arsenic with oxygen are rapidly absorbed, while the salts of oxide of antimony do so only with great difficulty.* Even after the injection of the latter metal into the blood, a long time passes before the occurrence of the symptoms of poisoning, provided that very large doses have not been used. Consequently the passage of the antimony from the blood into the tissues only takes place very slowly.

The smallest doses of arsenic are carried off by absorption from the point of application, and diffused in the organism, while antimony *lingers a long time in the stomach*, there stimulating the centripetal nerves in the mucous membrane in a peculiar manner, and reflexly *evoking vomiting.* That the latter has really this origin, and is not due to an action of the compounds of antimony upon parts of the central nervous system, follows from the fact that when tartar emetic is injected into the blood or under the skin far larger quantities are necessary to induce vomiting than is the case when it is given by the stomach (Gianuzzi, Radziejewski, L. Hermann and his school). Moreover, a far longer time passes in the former case before vomiting comes on than in the latter case. From the blood the antimony must first be poured out upon the mucous membrane of the stomach before it can evoke vomiting. This, however, necessitates a certain amount of time, and the employment of considerable quantities of the substance. When vomiting results after this method of administration, antimony is always found in the vomit, as has been shown by various investigators in past and in recent times.

Besides their caustic action, the *compounds of antimony can only be employed therapeutically as emetics and expectorants* in the same sense as apomorphine and emetine. All that has been said in this direction about the latter also holds good for *tartar emetic*, which is at present the preparation of antimony most usually employed. Only in those cases where it is desirable, for the sake of an expectorant action, that we keep up a uniform mild degree of nausea for a considerable time, is the *pentasulphide of antimony* more suitable than tartar emetic. It contains a small quantity of oxide of antimony, which is but slightly soluble in the acid of the gastric juice. Hence, the effect is of necessity never other than a mild one. In the intestine, through the action of alkalies, a formation of sulph-antimoniate probably takes place.

As in the case of pentasulphide of antimony, the action of a series of other insoluble antimonial preparations, which have almost fallen into disuse in every country—*e.g.*, mineral kermes and the native ter-sulphide of antimony—is dependent upon the presence of small quantities of oxide of antimony.

3. *Mercury.*

The *absorption of mercury* takes place in the form of soluble compounds with albuminous or other nitrogenous substances. Such combinations either form first at the point of application, or may be employed from the outset if a local caustic action is to be avoided. For subcutaneous injection in man those compounds of mercuric oxide are suitable which are soluble in alkaline fluids, and which are made with peptones (Bamberger), or with the amides and amido-acids of the fatty series, *e.g.* with acetamide, glycocol, and asparagin.

In consequence of the above-mentioned peculiar behaviour of oxide of mercury towards albuminous substances, even *quite insoluble compounds of this metal are absorbed.* Among the most important of these is calomel, which is never changed in the stomach into corrosive sublimate, nor in the intestinal canal into mercurous oxide, but which is simply dissolved by the albuminous substances, although only to a very small extent (Buchheim and v. Oettingen). This part may be played by the pepsin (Tuson) without its action as a ferment coming into question. The solution of the calomel takes place even in the subcutaneous cellular tissue, for in the pus of the abscess which is caused after its subcutaneous injection a soluble compound of mercury is to be found (R. Bellini).

Mercury causes its characteristic effects even when it is rubbed into the skin in the form of the so-called *grey ointment.*

The question as to *how mercury is taken up from the skin* cannot be answered with certainty. Grey ointment contains only very finely divided mercury, and, as a rule, the sub-oxide of it in the form of salts of fatty acids. Hence it was easy to leap to the conclusion that the latter alone got into the organism by means of the follicles of the skin. But this view is opposed to the fact that the actions of mercury come on even after the inunction of a grey ointment made with chemically pure mercury free from sub-oxide. Hence the older explanation of this process is still current, viz., that the fine granules of the metal penetrate through the skin into the tissue and into the blood, and are here transformed into an active combination. Much trouble used to be taken to prove the presence of the uncombined metal in the blood and tissues of animals. Some observers obtained thereby a positive result (Eberhard, Landerer, van Hasselt, Overbeck), and others quite a negative one (v. Bärensprung, Donders, Hoffmann, Rindfleisch). But even if the taking up of these granules by the skin were perfectly certain, the transformation of the metallic mercury into the active compound does not necessarily result only when it has got into the blood, but may occur on the surface of the skin under the influence of moisture and fatty acids through oxidation in the air.

Mercury causes the *blood-pressure to sink,* and paralysis of the vessels seems to have a share in causing this. Yet here the *paralysis of the heart* is much more prominent than in the case of poisoning with arsenic and antimony. After the injection into the blood of considerable quantities of the compounds of mercuric oxide with amido-acids (p. 174), the animals die from the direct effects of the cardiac paralysis.

In animals, however it be administered, *acute intestinal symptoms* can be evoked independently of the caustic action, these being tenesmus and watery or bloody dysenteric diarrhœa. When the poisoning has a more chronic course, we find in the intestine hyperæmia, hæmorrhagic erosions, and diphtheritic ulcers. In cases of poisoning in human beings, we find in the most acute form, which nevertheless always has a chronic character, catarrh of the stomach, colic, simple and bloody stools, and dysenteric affections of the mucous membrane. These intestinal symptoms, which are of uncertain origin, follow the external inunction even of the grey ointment (Brandis, 1870).

Simple stools and diarrhœa, without affections of the mucous membrane, come on regularly after the internal use of *calomel* and *mercurous bromide* in not too small doses. Since through the rapid supervention of diarrhœa the calomel is carried off again before any considerable quantity of mercury is absorbed, it follows that the action is purely local, and consists in a stimulation of the intestinal ganglia. At any rate, there is no great general irritation of the intestinal canal; consequently calomel is an excellent aperient, which is specially adapted to those cases in which, as in typhoid fever, the intestine itself is the seat of the ailment. In infantile diarrhœa, we expect from this remedy an *antiseptic action* as well as the evacuation of the decomposed contents of the intestines. As a matter of fact, the presence of calomel prevents the occurrence of putrefaction in artificial digestion, without prejudicing the action of the digestive ferments (Wassilieff).

A *beneficial influence upon the secretion of the bile* has been ascribed to calomel. Certainly the peculiar green colour of the "*calomel stools*," at times observed, owes its presence to their containing a copious supply of biliary colouring matter (Simon, Buchheim). Nevertheless, in *experiments on animals* with temporary or permanent biliary fistulæ, an increase or acceleration of the biliary secretion has but seldom been found after the administration of calomel (Nasse, Röhrig). As a rule this secretion experienced rather a decrease (Kölliker and Müller, Scott, Bennett, Rutherford). On the other hand, corrosive sublimate very considerably rouses the excretion of the bile, not after subcutaneous injection (Bennett), but after administration by the mouth (Rutherford).

Peculiar to mercury are those *effects upon the tissues and organs of the mouth*, which are so very noticeable. Amongst the many signs of the action of mercury, *salivation* shows itself regularly in human beings, though less often in animals. It is, in some cases at least, suppressible by atropine, and therefore takes place through the influence of the salivary nerves. With prolonged use of mercurial preparations, a *stomatitis* develops itself in human beings and in animals, and with this a bad smell in the mouth, especially in the human subject. This very readily leads to ulceration of the mucous membrane of the mouth and of the gums, to necrotic destruction of the soft parts of the jaw, to falling out of the teeth, and to swelling of the salivary glands. The origin of these affections is just as uncertain as that of the corresponding changes of the intestinal mucous membrane.

As in the case of the mucous membrane of the mouth and of the intestinal canal, the *external skin is frequently the seat of mercurial affections*, consisting in roseola, exanthemata, and eczemata.

Finally, besides the affections which arise as complications, mercury causes in chronic poisoning in man a *series of symptoms which affect the central nervous system.* To these, above all, belong the mercurial trembling which may lead to spasmodic movements in the limbs (*tremor mercurialis*). The psychical irritability, called *erethismus mercurialis*, which is often increased or invoked by the slightest emotions, and which is accompanied by sleeplessness, headache, and palpitation of the heart, is very singular. Here must also be included the diffused pains which are situated in various parts of the organism, as, for instance, in the neighbourhood of the joints.

In *animals* these cerebral symptoms are not well pronounced, yet trembling and indications of erethism in the form of terror show themselves, yet by no means constantly ; so that it is hard to decide whether it is a matter of the primary specific effects of mercury or the result of abnormal nutritive processes.

The *therapeutic importance of this metal* cannot be deduced from the action of mercury, sketched in the foregoing account, for, with the exception of the use of calomel as an aperient, we seek most carefully to avoid all these actions, even the salivation which appears as one of the first symptoms.

We are therefore compelled, as in the case of arsenic, to lay hold of the alterations of metabolism and nutrition.

Mercury plays the most striking part in the treatment of the *local secondary syphilitic affections*, of condylomata, hard chancres, and affections of the skin and throat. As to the utility and judiciousness of this method of treatment, opinions have been divided from the sixteenth century up till now. Considering the consensus of opinion, we may fairly assume that the above-mentioned syphilitic affections disappear more surely and more quickly under the use of mercury than under other methods of treatment.

We can only consider the process of the cure in syphilis as due to the effects of the metal upon the metabolic processes in removing the local affections, and, in consequence of this, interfering with the sources of the syphilitic poison. That the latter should be directly destroyed by the small doses of the metal which come into action in these cures, seems to be beyond the bounds of possibility.

Mercury is moreover used, especially in the form of inunctions of grey ointment, *in inflammations of the serous membranes*, *of the glands*, *and of the subcutaneous cellular tissue.* If the mercurial treatment is expected to cause successful results in these cases—a very difficult matter to judge of—all the less can it be a case of specific influence of this metal upon the syphilitic poison.

If, therefore, all the facts indicate that the therapeutic importance of mercury is to be sought for in its influencing, possibly in a special way, the metabolic processes in general, and the nutritive conditions of the organs in particular, it is nevertheless impossible to see into the nature of this metabolic action. This is because in regard to this action there is known to us but a small number of unconnected facts, amongst which, moreover, the secondary are hardly to be separated from the primary effects.

In connection with this, *the origin of the so-called mercurial cachexia* is still uncertain; it occurs along with the numerous local ailments, in the form of anæmia, emaciation, and all sorts of general complaints seen in chronic mercurial poisoning in man. It is at any rate doubtful whether it has an independent importance, or owes its origin only to local ailments. As a rule no great weight is to be laid upon the *blood analyses* carried out for the purpose of explaining these nutritive disturbances.

For a different reason special attention is deserved by the observation first made in the human subject, and confirmed by experiments on animals, that under the use of small doses of mercury *the weight of the body increases, and the number of the red blood corpuscles rises* (Liègois, Keyes, Bennett, Schlesinger). We have, therefore, here to do with an apparently favourable influence upon the nutritive relations, similar to those which are found under certain conditions after the use of small doses of arsenic.

As to the *behaviour of metabolism* under the influence of mercury, little is known. In the case of a man suffering from syphilis, and who was in a state of nitrogenous equilibrium, the excretion of nitrogen was neither increased nor diminished when grey ointment was rubbed in, till salivation ensued (v. Boeck).

Among the results of the action of mercury, there deserve to be mentioned the *fatty degenerations* in the organs, and a *diabetes* which only comes on slowly in rabbits and dogs, after the subcutaneous injection of corrosive sublimate; this lasts at times from four to eight days, and has been observed in man in cases of chronic mercurialism. The copious deposits of lime in the kidneys are peculiar (Salkowski); they occur in man and animals, and seem to be connected with decalcification of the bones (Prevost).

The *diffusion* of the absorbed mercury through the organs, and its *elimination out of the body* has been subjected to a thorough investigation. The elimination takes place mainly through the urine, and, by means of the bile, through the fæces. It lasts a considerable time after the last dose, and is subject to great irregularities. The use of iodide of potassium seems, according to recent investigations, to have no influence upon the elimination of it (Vajda and Paschkis).

The choice of the individual preparations of mercury, for the purpose of attaining a constitutional action for therapeutic purposes, adapts itself essentially to the way in which it is desired to administer them. *Calomel* answers for internal use; it remains, however, a long time in the digestive canal, and hence readily causes diarrhœa and other symptoms in the stomach and intestine. For employment in the form of subcutaneous injections, the above-mentioned *amid-, amido-, and peptone-compounds of mercuric oxide* may be chosen; these may be made from corrosive sublimate by mixing a solution of it with the corresponding nitrogenous compounds, and neutralising the fluid with carbonate of soda. In animals, after the hypodermic injection of corrosive sublimate, the above-mentioned form of inflammation of the kidneys results, and albumen appears in the urine (Salkowski). Consequently, in man, when compounds of mercury are injected subcutaneously, we must remember the possibility of the occurrence of renal affections. *Grey ointment* is used for *inunctions*: these are indicated in those cases in which we wish as far as possible to avoid disturbances of the digestive canal, and where we dread the subcutaneous application on account of the renal affections.

4. *Iron.*

On account of its occurrence in the hæmoglobin of the red blood corpuscles, iron plays from a physiological point of view an important part, and consequently as a remedy takes a special position among the heavy metals. In its pharmacological behaviour, on the other hand, it exhibits the greatest agreement with them. After the *injection of alkaline solutions of it subcutaneously*, it is absorbed in great quantities, and causes *renal affections* as above mentioned. After its injection into the blood, the *blood-pressure* falls, and intestinal symptoms supervene, which in regard to their character and origin perfectly resemble those which are evoked by arsenic and antimony. Along with this, in mammals and in frogs, *disturbances of the voluntary movements* come on, which are dependent upon paralysis of the central nervous system.

Finally, too, as after other remedies which some time before death lower the circulation through great reduction of the blood-pressure, the quantity of the *carbonic acid in the blood* becomes very greatly reduced (Meyer and Williams).

All these effects and their consequences are absent, if iron, no matter in what form, be brought into the *healthy stomach*, provided it does not injure the latter by its caustic action. If the metal gets into the blood through being administered subcutaneously, it passes rapidly over into the urine, and can be found in the latter by the usual reagents, especially by sulphide of ammonium. But this reaction of iron in the urine is, as a rule, entirely absent after its internal use in medicinal doses, and in experiments made by feeding animals with it (Becquerel, Jhering, Hamburger).

The absorption is so small that a dog on being fed with sulphate of iron daily excretes in the urine only 1 to 2 mg. ($\frac{1}{16}$ to $\frac{1}{30}$ grain) of iron more than he does with a pure flesh diet (Hamburger). Since when large quantities of iron are taken up into the blood renal inflammation results and the metal appears in the urine, and since this does not result when it is given by the mouth, it follows that, when applied in the latter manner, the mere traces of iron which pass into the urine are, as a matter of fact, dependent upon the absence of the absorption, and not upon the metal being first absorbed into the blood and then excreted through the bile into the intestine.

In this state of affairs it is impossible to speak *of the actions* of the iron preparations upon the vascular or central nervous system, or upon other organs *when they are employed medicinally.*

Since a free administration of iron by the mouth causes no noticeable increase in the amount absorbed into the blood, provided cauterisation of the mucous membrane of the stomach does not occur, we cannot assume any special action of this metal upon metabolism, *i.e.*, an action situated beyond the physiological boundaries. The alterations observed in metabolism, and which are said to consist in an increased excretion of urea or of nitrogenous substances (Rabuteau, Pokrowski), are consequently to be referred to any cause other than a general iron action. The case is similar with the excitation of the vascular system, so dreaded after the use of iron, and with the tendency to hæmorrhage which supervenes, just as after the misuse of acids. The assumption that a rise of blood-pressure amongst other things is at the bottom of these symptoms is quite an arbitrary one.

On the other hand, the *local changes* which the compounds of iron evoke in consequence of a mild caustic and astringent action upon the *mucous membrane of the stomach*, may exercise indirectly a considerable influence upon nutrition, seeing that they, according to the strength and duration of the action, sometimes interfere with the processes of digestion and absorption, and disturb the general nutrition; and at other times aid in improving a persistent ailment of the mucous membrane of the stomach, and through this become of use to the nutrition, as has always been insisted upon in every direction.

The special action of iron does not, therefore, according to our present state of knowledge, come into consideration from a therapeutic point of view. The whole iron question consequently hinges upon whether the small doses of the metals which are absorbed after their medicinal use are in a position to favour a *multiplication of the red blood corpuscles*, in those cases in which their number is morbidly decreased, relatively and absolutely.

Under normal circumstances, and *with the usual diet*, *far more iron* is carried to the organism than the latter under any condition needs, even for the increased formation of blood after hæmorrhages, and during the rapid growth of youth. In the case of a child, of the iron taken in with the milk, barely the half was used for the body (Hösslin). An adult man contains in his whole body about 3 grammes (46 grains) of iron, while 0·06–0·09 g. (1 to 1½ grains) is supplied to him daily with his food, *i.e.*, a very important part of that amount. Hence an otherwise healthy man recovers after the greatest loss of blood, when not fatal, without the use of iron, provided the food be sufficient.

The therapeutic importance of iron consequently becomes still further restricted; only those cases remaining to be considered where, in consequence of chronic affections, the *amount of blood and the number of the red blood corpuscles or the amount of hæmoglobin contained in the latter* has *suffered a diminution.*

The greatest benefits have been ascribed to the *use of iron in chlorosis*, where the reduction of the number of red blood corpuscles, or the amount of hæmoglobin in them, forms not only a part of the symptoms of the general disturbances of nutrition, but seems to have a certain independent importance. Since the epoch-making blood analyses of Andral and Gavarret, it has been shown by a large series of investigations that in chlorosis, with suitable diet, the number of the red blood corpuscles and the amount of the blood colouring matter increase after the use of iron; nevertheless, in the typical cases of this affection, there is hardly any need of these analyses to prove this fact, for the same is proved by the cheeks of the chlorotic girl becoming red under its use, in place of being waxy pale, as their owners get restored to health. Whether the iron helps in this has not been decided, notwithstanding the firmly rooted belief in it. Certainly, to begin with, the possibility cannot be denied that under conditions otherwise favourable and necessary to the cure, the formation of the red blood corpuscles may be forced, even by an increase of the amount of iron absorbed, which, though in itself minute, is kept up a considerable time, because of a long-continued extra supply of the metal. Yet, up till now, proofs resting upon an experimental basis are still wanting to support such a view.

If the usefulness of iron in the treatment of chlorosis is more than doubtful, its employment as a *tonic in anæmia and general wasting*, such as are caused by chronic diseases, seems even less based upon well authenticated successes, setting aside the cases in which, *hrough improving morbid states of the mucous membrane of the stomach* n the manner above described, a favourable influence is exerted upon the digestion and nutrition. The preparations of iron are, however, not employed methodically as local remedies for the stomach; in this direction they are inferior to the basic nitrate of bismuth.

Perchloride of iron answers as an energetic *hæmostatic* in superficial hæmorrhages where ligature of the vessels cannot be effected. It owes this application to its property of readily causing the coagulation of blood which has not lost its fibrin; in this action the acid and the metallic oxide co-operate simultaneously. We must not, however, believe that because it can stop bleeding in the stomach, it is also possible to treat hæmorrhages in the lower part of the intestine successfully, for it does not reach so far, but becomes converted beforehand into ferric albuminate and sulphide of iron, which are naturally quite inert in this direction. In former times an influence upon the hæmorrhages of internal organs, *e.g.*, the uterus, was ascribed to chloride of iron administered by the mouth.

In regard to *Manganese* we can only say that it has been tried therapeutically in various, especially "diathetic," affections. When injected hypodermically it is a powerful poison, for it causes more particularly inflammation of the kidneys, yet hardly a trace of it is absorbed from the stomach and intestine (Kobert).

5. *Silver.*

The *compounds of silver*, as employed in therapeutics, are to be considered entirely *as local remedies*, although they are very poisonous when injected hypodermically or into the blood in a non-caustic form, *e.g.*, in the form of solutions of chloride of silver in hyposulphite of sodium.

According to the investigations of Bogoslowski, Ball, Rouget, Curci, and Jacobi, the action seems to consist mainly in *paralysis of the central nervous system*, by which, to begin with, the posterior halves of the body are affected so that the animals trail their hind quarters after them. The occurrence of profuse secretion from the bronchial mucous membrane is very striking (Orfila, Ball, Rouget). The animals succumb at times in convulsions, due to insufficiency of the respiration. Whether these are brought about by paralysis of the respiratory centre, or in consequence of œdema of the lungs, has not been decided. In *frogs* convulsive spasms occur before the general paralysis; the twitchings of the muscles come on and the heart stops in diastole (Curci).

That the *compounds of silver* are absorbed, at least in small quantities, *from the stomach*, is proved by the deposits of finely divided silver in the skin and in many internal organs, observed in man after continued use of nitrate of silver, and experimentally brought about in animals under similar conditions. In consequence of this, these parts exhibit the dark coloration known under the name of *Argyria.*

The particles of silver occur in the *skin* in the upper layer of the corium (Frommann, Riemer), in the sweat glands, and in the smooth muscular fibres (Riemer). In animals, especially rats (Huet), and in dogs (Ball and Charcot), the coloration of the skin is absent.

In the *intestinal canal* the metals are deposited in the tissue of the mucous membrane, but especially in the villi of the small intestine; the *epithelium* is everywhere free of it, even in the skin. Among the remaining organs the following parts are distinguished for *copious deposits*—the glands of the mesentery, the choroid plexus of the brain (Frommann, Riemer), the articular villi (Riemer), in rats, the duodenal part of the mesentery (Huet), the intima of the aorta (Riemer), the liver, and the kidneys. In the *liver* numerous deposits of silver are distributed throughout the walls of the finer twigs of the vena porta and small hepatic veins (Frommann), in the vicinity of the hepatic ducts and arteries, as well as through the ground substance of the connective tissue between the acini (Riemer). In the *kidneys* the glomeruli are the most important seat of the deposits, even in rats; yet they are not wanting in the pyramids, and especially in the papillæ, and are here embedded upon and between the walls of the straight urinary tubules (Frommann, Riemer, and Huet). In the substance of the brain and spinal cord no deposit of silver was to be found (Riemer).

The *absorption of silver from the stomach* takes place at all events only very slowly. Any effects which may result when silver is thus administered are not known *in man.* Even two *rats*, which received for more than a year 5 to 6 mg. ($\frac{1}{12}$ to $\frac{1}{10}$ grain) a day of nitrate of silver, showed no disturbances whatever of their health, and the kidneys no sign of nephritis (Huet). On the other hand, in the case of *rabbits*, after long-continued feeding with small doses of the double hyposulphite of sodium and silver, and with silver peptone, *symptoms of paralysis* showed themselves in the posterior extremities (Bogoslowski). When nitrate of silver was given under similar conditions, the rabbits died from emaciation, and, along with fatty degeneration in the various organs, the above described degenerative changes were found in the kidneys (Rószahegyi).

Statements are divided in regard to the *occurrence of silver in the urine after internal use.* Aside from some previous positive results, Mayençon and Bergeret profess to have found it recently by electrolytic methods. Jacobi, on the other hand, could not find the metal in the urine of rabbits, even when it was administered for a considerable time subcutaneously.

The *reason why the compounds of silver have but a slight* action when taken medicinally, or when given to animals, is mainly to be found in the fact that the metal becomes for the most part reduced, and then deposited very soon after its transit through the walls of the intestinal canal (Jacobi).

If *in man no one has ever observed anything but local alterations* after the internal use of nitrate of silver, one must not expect (*a priori*) any therapeutic results dependent upon an action on the nervous system. Experience in practice seems to entirely confirm this conclusion.

Silver is used even at the present day in *various diseases of the nervous system*, especially in *epilepsy*, and *progressive paralysis of the spinal cord.* It was formerly also very much used in St. Vitus' dance, mania, and hysteria. According to Labavius, this use of it descends from the time of the caballa, when it was believed that silver behaved towards the morbus cerebri lunaticus just as the luna to the brain (Krahmer).

This neurotic drug in the course of time has had to pass through *great vicissitudes.* While it was recommended most warmly by some physicians, others rejected it just as decidedly. For a time it fell even totally into oblivion, but only to appear once more. At present its use as a neurotic is again on the wane, but will probably increase again, as has been always the case.

One part of the unabsorbed silver is *reduced even in the wall of the stomach and intestine*, and is deposited upon the mucous membrane, immediately under the epithelial layer, in the form of black granules. In this way there results a *diffused argyrosis of the intestinal canal* (Jacobi). It is quite fair to ask whether such a *silvering of the intestine* has any importance from a therapeutic point of view. Nitrate of silver, which acts so decidedly as a caustic, and at the same time as an astringent, is much employed and with good success, not only in *catarrh of the stomach, but also in chronic catarrh of the intestine.* It is hard to believe that the nitrate gets into the intestine in the unchanged condition, and here exerts a peculiar astringent action, because in the stomach it must be transformed into an albuminate, or into chloride of silver. Meanwhile the question as to the import of such a silvering cannot be answered.

As regards the employment of silver *as a local remedy*, there is nothing special to add to what has been said above. Still less is it necessary to enumerate the cases in which this remedy has specially shown its value. The rules for the requisite strength and duration of its action must be formulated by medical experience.

Since the compounds of *Gold* are more readily reduced than those of silver, so no kind of general action is to be expected from its preparations when employed internally; moreover, it is of no importance as a local remedy.

6. *Copper and Zinc.*

The pharmacological connection existing between copper and zinc follows not only from the similar behaviour of their easily soluble salts at the points where they are applied, but depends above anything else upon the similar actions which they evoke after the injection of their non-caustic double compounds into the blood or subcutaneously.

These actions consist in *paralysis of the voluntary muscles and of the heart*, and bring about death by arresting the action of the latter.

Whether zinc exercises, moreover, *a direct effect upon the central nervous system* is for the present still undecided. The sole symptoms which point to such an action are disquiet, terror, and an inclination to gnaw in rabbits. These also occur along with vomiting and diarrhœa, when various kinds of animals are fed for a long time with oxide of zinc, and they are accompanied by twitchings of the limbs, and at times by convulsions (Michaelis).

Chronic cases of poisoning by copper and zinc, properly so-called, are not known in man. It was even impossible to cause an action of copper experimentally, either in attempts made by men upon themselves or upon animals. In the latter, experiments at feeding with copper salts were almost quite negative (Daletski and Pelikan, Galippe, Burq and Ducom).

After large internal doses of the acetate and of other salts of copper with fatty acids, the animals succumbed to paralysis of the heart, with disturbances of respiration (Falck and Neebe), probably because in these cases a caustic action upon the mucous membrane of the intestinal canal had favoured absorption. After the subcutaneous injection of acetate of copper in rabbits, inflammation of the kidneys resulted, and albumen was found in the urine (Koeck).

The *compounds of zinc* are employed *in nervous diseases*, in similar cases in which silver is used, especially in epilepsy and neuralgic affections. Although, according to experiments on animals, the possibility of an action of this metal upon the nervous system, even after internal administration, cannot be denied off-hand, yet there is no rational or good empirical ground for such a use of it.

The continued contradiction of *opinion as to the utility of this remedy* in the affections named, and the want of critical investigation, at present prevent our arriving at a judgment as to the state of affairs, which is free from subjective convictions, and yet based upon experience. In case of further therapeutic trials of it, everything will depend upon the employment of such a method of administration as will make the absorption of the zinc quite certain. At the same time, however, there must be kept in view the risk of *inflammation of the kidneys*, after the subcutaneous injection of non-caustic double salts.

The salts of zinc and copper cause vomiting in the same way as the compounds of antimony. *Sulphate of copper* alone finds extensive employment in this direction. When the latter gets into the stomach, vomiting comes on before the caustic action, and brings about at the same time the evacuation of the salt. Consequently we may employ large doses to ensure the result, without needing to fear the occurrence of an injurious caustic action. Since, moreover, there is no reason to fear undesirable effects dependent upon the absorption, sulphate of copper will retain its position as an emetic alongside of apomorphine.

As an *expectorant* this salt is not suitable, because the very transitory nausea and the rest of the coincident symptoms do not readily occur without the supervention of vomiting.

Various compounds of both metals are used as *local remedies.* *Oxide of zinc*, in the form of an ointment, in which it is united with fatty acids in small quantities, is a gentle astringent; presumably oleate of zinc mixed with fat would be more suitable.

Chloride of zinc is a pure caustic and is adapted for surgical purposes in those cases where a firm eschar is to be avoided, and in which the deeper penetration of the remedy is desired. Moreover, when the caustic is employed to disinfect wounds, a sharp limitation of the action through a firm eschar must not occur, because infective substances may readily remain behind under the latter.

The *sulphates* of both of these metals are of service in those external affections in which we wish to evoke simultaneously a superficial destructive cauterisation and transitory stimulation, followed by an astringent action.

7. *Lead.*

The effects of lead due to its absorption can be only brought about in the most acute form by the help of its carbon compounds, *e.g.*, lead triethyl; they *affect* the *intestine*, *the muscles*, *and the central nervous system.*

In *frogs* the *muscles* are brought by the lead first into a condition in which they *tire out rapidly* when kept in continuous action, yet they do not show any loss of irritability. When this action has reached its acme, the muscle gradually loses also its irritability, and then dies entirely, only a moderate degree of *post mortem* rigidity occurring. Even before this the *heart* comes to a standstill in consequence of being paralysed.

Likewise in *rabbits* the *muscular paralysis* predominates and extends to the heart; the animals succumb under the effects of this action. As regards *cats* in slow poisoning by lead, paralytic symptoms come on, which are probably dependent upon a muscular affection. In *dogs* nothing of the latter can be seen.

It cannot well be doubted that *lead palsy in man* is to be considered as a direct effect of this metal; degeneration of the muscles, however, gradually supervenes upon the original simple action of the *poison.* The irritability of the *muscles* for the interrupted induction current vanishes, or at any rate is lessened, while for the constant current and for mechanical stimuli it remains intact, or even increases.

The *cerebral symptoms* can be easily produced *in dogs.* They consist in peculiar chorea-like movements, which may even amount to regular convulsions, without impairment of the sensibility and consciousness. The animals ultimately succumb through the effects of paralysis of the motor areas of the central nervous system. The above-mentioned symptoms of irritation are also observed in *cats and pigeons.* A part of the symptoms which form the *encephalopathia saturnina* in man, and among these the epileptiform spasms united with coma, are undoubtedly direct effects of the lead, while another part of these, especially the states of mental excitement and depression, the headache, and the amaurosis, are to be considered, like the symptoms of chronic alcoholic poisoning, as results of a protracted primary action.

The *arthralgia saturnina*, which constitutes in man a frequent form of ailment in chronic lead poisoning, has not been observed in animals. The symptoms of the arthralgia are violent pains in the joints and the adjacent muscles, as well as spasmodic contractions of the latter, which in the extremities often affect the flexors, in the trunk the extensors of the back, and in the thorax all the muscles : as to the origin of this, nothing definite can be stated.

Through the *acute action of lead* upon the intestine increased peristaltic movements and spasmodic contractions of the intestinal tube, with violent colic, are evoked in dogs and cats, but in rabbits only simple diarrhœa. Since the intestine can be brought again to a state of *rest* by atropine, the contractions are dependent upon an irritation of the motor ganglia of the intestine.

In *lead colic*, which is in man the most common form of ailment in chronic lead poisoning, the spasmodic *contractions of the intestine* play the chief part. Nevertheless, in other abdominal organs also, spasmodic states seem to occur which are directly dependent upon the action of the lead. In neighbouring organs the spasms may occur reflexly. The *nature of the pulse*, which is slow, full, and hard, depends apparently upon the accumulation of the blood in the remaining vessels, brought about by the compression of those of the intestine.

All preparations of lead, even those which are quite insoluble in water, such as the sulphate, cause chronic poisoning in man and animals, when they are administered for some time *per os* or hypodermically.

The *absorption of lead* takes place *but* slowly from the intestinal canal, and yet in fairly large quantities (Annuschat). The *excretion* takes place by the urine and the bile. The latter contains the metal only when freely administered, although it occurs in the liver even in the opposite case (Annuschat). In rabbits it can be found in the urine the next day, if it has been brought into the stomach in a dose of 3 to 4 mg. ($\frac{1}{20}$ to $\frac{1}{15}$ grain) of the soluble salts (v. Lehmann). The use of *iodide of potassium favours the passage* of the lead into the urine (Melsens, Oettinger, Annuschat, &c.).

The above described *actions of lead* have only a *toxicological importance;* for therapeutical purposes they are not made use of. The compounds of lead are only used at present as *local astringents;* as to the importance of which all that is necessary to say has been already said. But it must be remarked that they are to be avoided in affections of the stomach and intestine, or only to be used with the greatest caution, and especially not for too long, because in consequence of the absorption chronic lead poisoning may result.

It is not long since it was believed that by giving acetate of lead internally it could be caused to act upon distant organs, as, for example, as a hæmostatic in hæmorrhage from the lungs, and as an astringent in their inflammations.

8. *Bismuth.*

General effects on the part of this metal have only been obtained in animals quite recently. In acute cases these concern the central nervous system, especially the medulla oblongata, and in more chronic cases affect the intestinal canal (H. Meyer and Steinfeldt). As to the local action of nitrate of bismuth, and its importance in the treatment of stomach and intestinal affections, what is necessary has been already said.

9. *Aluminium and its Compounds.*

As regards their local action, all the soluble salts of aluminium act like the salts of the heavy metals. They form albuminate of aluminium; and the nature of this substance causes them to be powerful *astringents*, hence they may be administered internally to the mucous membrane of the stomach and intestine, because they do not, like the salts of lead, give rise to poisoning through being absorbed.

The *passage of alumina from the stomach into the blood* does not appear to result to any material extent. Of an astringent action in the lungs, kidneys, or other organs, proceeding from the blood, there is not the slightest possibility, even if we set aside the fact that alumina, like the metallic oxides, cannot act as an astringent in the form in which it occurs in the blood.

Of all the salts of aluminium, *potash alum* is the one preferred in practice for employment as an universal astringent in all sorts of cases. On account of the weakly basic properties of alumina, in contrast with the double compounds of the heavy metals, it has a very decidedly *acid* reaction, and consequently behaves at the seat of application, just as the simple metallic salts do. Employed in excess, alum and the other compounds of aluminium cause inflammation; if the latter is associated with much exudation, we do not need to conceive a special liquefaction of the albuminous fluids by the alumina, as Mialhe does.

Since alumina can precipitate albuminous and many other organic substances, its salts act as very decided *antiseptics*. For the disinfection of latrines, drains, and the like, chloride of aluminium has been recommended, and it has been introduced into commerce under the name of chloralum. It is quite a suitable preparation if the price does not prevent its being used in sufficient quantities.

10. *Phosphorus.*

Phosphorus from the nature of its actions is to be ranked pharmacologically, on the one hand, with the muscle and nerve poisons, and on the other with arsenic and the heavy metals.

The common variety, the so-called *yellow phosphorus*, is only *absorbable* in proportion to its volatility at the temperature of the body, and to the solubility of its vapours in watery fluids. In this the bile also comes into consideration as a solvent of phosphorus (Buchheim and Hartmann). Nevertheless, when taken internally, its absorption results very slowly, and the symptoms of poisoning develop only gradually, and mostly after the lapse of several days.

The only known localised action is a *paralysis of the heart*, and this often causes death quite suddenly (H. Meyer). Independently of this, there come on *alterations of metabolism and disturbances of nutrition* in the most widely different organs. These disturbances of nutrition consist in fatty *degeneration* of the liver, of the kidneys, of the cardiac muscle, and also of the other striped muscles; and further, in *ecchymoses* into the mucous and serous membrane, and in inflammation of the glands of the stomach (*gastro-adenitis*). In animals, alterations are caused in the bones similar to those caused by arsenic, viz., *dense osseous substance* replaces the spongy (Wegner).

The *influence of phosphorus upon the total metabolism* is very energetic. The quantity of urea lessens (Schultzen and Riess), while the nitrogenous excretion is increased (Storck, Bauer, Falck). In the urine the nitrogen occurs in the form of various products, amongst which there are at times leucin and tyrosin, but more especially peptone-like substances. Moreover, the urine contains sarco-lactic acid (Schultzen and Riess).

These facts cause us to believe that the essence of this alteration of the metabolism consists in an increased breaking up of the constituents of the body, and in inhibition of the transformation of the resulting substances into the normal final products of metabolism.

These actions yield *no rational indications* for the therapeutic employment of phosphorus, excepting for the formation of firm osseous substance. Even the trials of the remedy in the most widely different affections have till now led to no empiric indications. The dangers attending the use of phosphorus do not at present justify the retention of this powerful poison in therapeutics. Red amorphous phosphorus, being neither volatile nor soluble in any fluid, is consequently quite harmless.

CHAPTER VI.

THE GENERAL ACTIONS OF THE AROMATIC COMPOUNDS.

The substances of the aromatic series form neither a special group nor a peculiar class of pharmacological agents, but show in their behaviour in the organism, and as regards their action upon simply organised beings, the same fundamental character, so that, for the sake of review, a comprehensive treatment of them seems justifiable.

The *behaviour* common to all *of the compounds of the aromatic series in their transit through the body* depends upon the stability of their benzol nucleus. It has not been proved in any case with certainty that it is ever destroyed in the animal body. On the other hand, the side chains, composed of bodies belonging to the fatty series, when they are attacked, generally undergo analogous changes to what occur in those cases where they enter the body unassociated with the benzol nucleus; with the limitation, however, that the "carbon atom, united with the benzol nucleus, is never separated from it."

The changes which the aromatic substances experience in the body can be explained by *oxidations*, *syntheses*, *decompositions*, and, in a limited degree, by *reductions*.

These processes, and the manifold products arising from them, offer great interest, but have attained as yet no therapeutic importance, except in quite restricted cases.

1. THE NON-NITROGENOUS AROMATIC COMPOUNDS AS MUSCLE AND NERVE POISONS.

The *hydrocarbons* of the aromatic series exercise no very striking action upon the central nervous system. The most energetic are the *turpentine oils*. The *actions* which follow their absorption in large quantities are to be interpreted in much the same way as the alterations which these and other volatile substances cause at the seat of application.

As in the case of the latter, so in that of the sensory nervous apparatus, stimulation may be caused if large quantities of these volatile substances get into the blood, and thence penetrate into the tissues. To such stimulation of the spinal cord, and especially of the vascular and respiratory centres, must be referred the rise of blood-pressure, the acceleration and spasmodic character of the respiration, as well as the increase of reflex irritability (Kobert) observed in animals after *large doses of turpentine oil.* If the reflex irritability seems originally diminished, this probably depends upon the fact that the stimulations at work in every direction bring about a reflex inhibition. The greatest doses cause ultimately general paralysis, in which, under the form of narcosis, the brain very early participates. In man these effects of turpentine oil cannot be evoked without great irritation at the point of application.

The *camphors* form a special group of aromatic substances, and are distinguished by their stimulant action upon the functional centres in the medulla oblongata. They have already been discussed under the nerve poisons.

Closely related to the pharmacological camphor *group* is that of *picrotoxin.* The latter embraces a number of non-nitrogenous substances belonging to the aromatic series, amongst which are picrotoxin, contained in cocculus indicus grains, the poisonous constituent of *water hemlock*, named *cicutoxin;* further, *coriamyrtin*, which occurs in the coriaria myrtifolia; and finally, the decomposition products of digitalin, of digitaleïn, of digitoxin, and of oleandrin. These all cause slowing of the pulse, rise of blood-pressure, spasmodic respiratory movements and convulsions, through stimulation of the origins of the inhibitory fibres of the vagus, of the vascular and respiratory centres, as well as of the motor areas of the medulla oblongata.

PHENOL, OR CARBOL (*carbolic acid*), which is easily absorbed from the point of application, even from the external skin and from the surfaces of a wound, acts *chiefly upon the medulla oblongata.* After the preliminary irritation there very soon follows paralysis. The twitchings and *spasms* observed in various kinds of animals depend to some extent upon a tetanising influence upon the spinal cord. The irritation of the respiratory and vascular nervous centres shows itself by *frequent and dyspnœic breathing* and transitory *rise of blood-pressure.* The latter has been observed after slow absorption of phenol from the skin (Hoppe-Seyler). Injection of a solution of carbolic acid into the blood causes, on the other hand, from the outset paralysis of the vasomotor nervous centres, and *great sinking of the blood-pressure*, without any appearance of alteration in the *activity of the heart* (Gies.) The *frequency of the pulse* is influenced by the twitchings and convulsions.

In the case of *human beings*, *cerebral symptoms* show themselves in carbolic acid poisoning. At first, headache, giddiness, weariness, and discomfort in the head come on, and then follows stupor.

In *animals*, along with the above leading effects, *sensory and motor disturbances* show themselves. The latter are not to be explained merely as results of the respiratory and circulatory disturbances.

And furthermore, *increased perspiration and salivation*—the latter in a prominent degree in animals—have also been observed as effects of carbolic acid. Whether atropine puts away these hyper-secretions is not known. The cough which at times sets in under the use of carbolic acid is probably dependent upon an *increased secretion of mucus* in the bronchi.

Death results in man and animals with symptoms of collapse, and is due to simultaneous paralysis of the respiratory and vascular nerve centres, and cannot be warded off by artificial respiration.

Moreover, carbolic acid is a powerful *caustic*, which, when given internally, readily evokes pain in the stomach, loss of appetite, nausea, and vomiting, and, in cases of poisoning with it, even gastro-enteritis. On the skin, concentrated solutions of carbolic acid elicit a burning pain, and cause *shrinking* and detachment of the epidermis. At the same time the part affected assumes first a red, and then a brown coloration. Under the action of the undiluted substance, a dry eschar results, which falls off without suppuration.

Carbolic acid owes its caustic action to its property of causing albuminous substances to coagulate, especially in the living organism. Other phenols and some di-phenols have the same effect.

After its passage into the blood, phenol unites with sulphuric and glycuronic acid, in which process it becomes partly transformed into the di-oxy-benzols (pyro-catechin and hydro-chinon). Moreover, these two appear in the urine in "*conjugation*" with sulphuric acid. After the urine has been passed, the di-oxy-benzols become free through decomposition of the conjugate compounds, and, undergoing oxidation in the air, yield products which are the cause of the dark colour of the phenol urine.

Effects upon the nervous system similar to those due to carbolic acid are caused by the three *di-phenols*—pyro-catechin, hydro-chinon, and resorcin. The first of these has the strongest action (Brieger), but all are less poisonous than carbolic acid.

Of the acids of the aromatic series, salicylic and benzoic acid are of chief importance from a practical point of view. The latter is not very active; but, on the other hand, after large doses of the former, especially when the rapidly absorbed sodium salt is employed, symptoms of collapse are in the human subject not unfrequently observed. The action of the salicylic acid upon the nervous system exhibits essentially the same fundamental character as that of carbolic acid. The same is true of many other aromatic compounds.

Salicin, for example, causes in animals convulsions, fall of blood-pressure, and, finally, stoppage of the respiration (Marmé), just as does carbolic acid.

Many nitrogenous aromatic compounds, especially aniline and chinoline, and, their simpler derivatives, rank with the nitrogenous substances as regards this character.

2. The Aromatic Compounds as Disinfectants and as Protoplasmic Poisons.

In the year 1832 Reichenbach obtained a fluid from wood tar which he named *creosote*, and which subsequently proved to be a mixture of phenols and phenol ethers.

Since creosote occurred also in smoke, and the latter could preserve meat and other animal products, Reichenbach came to the conclusion that the above substance was the antiseptic constituent of smoke, and found this view confirmed by subsequent experiments. The same antiseptic properties were exhibited by carbolic acid, which was shortly after obtained by Runge from coal tar.

Although in former times tar and other products of dry distillation were employed as antiseptics, and although creosote also was afterwards recommended in putrescent ulcers "to prevent the putrefaction of the secreted material," these facts obtained little attention, and it was reserved for quite recent times to concede an important *rôle* in the surgical treatment of wounds to carbolic acid and other aromatic substances.

We know now that *numerous compounds of the aromatic series are more or less disinfectant*, and that it is merely a question of choosing the remedy suited for one or other object, and of testing newly discovered substances in this direction.

The disinfectant action of the aromatic compounds depends upon the fact that they, as already stated in the case of quinine, exert a *deleterious effect upon the protoplasm* with which all vital appearances are ultimately connected. Even the simplest structures of the organic world, and in which life is only indicated by motion and metabolism, are subject to this influence on the part of the substances in question; consequently, many of these are employed with success for the purpose of preventing and destroying the development of fermentative and putrefactive organisms.

The action is, in most cases, not really a chemically destructive, but rather a *molecular one.* Even carbolic acid, which causes albumen to coagulate, does not form any compound with it (Bill).

Consequently, in contrast with chlorine and the metallic salts, the disinfectants of this category offer the, in many cases, important advantage that they are *not fixed to the albuminous substances* in the putrefactive and fermentative mixtures, and therefore are not rendered inert, but, unimpeded, can develop their poisonous influence upon bacteria and other low organisms.

Carbolic acid or phenol is the most energetic of all the substances of the aromatic series. In fluid and solid mixtures of organic substances, fermentative and putrefactive processes are suppressed, or their occurrence prevented, if they contain from ½ to 1 per cent of carbolic acid. As regards strength of disinfectant power, the remaining phenols rank next to the latter. Among these, *pyrocatechin*, *hydrochinon*, *resorcin*, *pyro-gallol*, and especially *thymol*, have become of practical importance. They act less powerfully than carbolic acid, but nevertheless with sufficient strength to promise good results in suitable cases. Pyro-gallol suppresses fermentation and putrefaction in quantities of from 1 to 3 per cent (Bovet). Of the almost insoluble thymol at least enough must be added to the materials to be disinfected to keep them continuously saturated with the remedy.

Among the aromatic acids *salicylic acid* is the most energetic, then follows *benzoic acid.* The remaining acids hardly come into consideration for practical purposes, because of their high price.

The *hydrocarbons*, because of their insolubility in water, can only have strongly antiseptic effects when they are very volatile at the ordinary temperature, and when consequently their vapours impregnate the objects to be disinfected ; but there must always be employed a great excess of the agent, *e.g.*, of naphthalin, in order that the vapours may develop for a long time in full concentration.

The *selection of the individual disinfectants* depends essentially on the objects which are to be disinfected.

When *masses of refuse* are to be treated, *e.g.*, human dejections, the contents of latrines, &c., the selection of disinfectants is only limited by their cost; hence we would not employ pure carbolic acid, not to mention the other chemically pure substances, but would be content with the crude constituents of tar, which have no disadvantages of any kind.

If, on the other hand, *dwelling-rooms*, *larders*, *house utensils*, *clothes*, and other articles in common use are to be disinfected, care must be taken that these objects are not injured by the remedy employed, and that they are not contaminated with such firmly adherent ill-smelling substances as phenol. The employment of this substance is consequently on the whole a limited one.

Aside from their disagreeable smell and taste, most of the disinfectants are excluded from use as *additions to foods and drinks*, because of their poisonous actions on the body. Of the above-mentioned substances salicylic acid alone is at the present day employed for these purposes. Nevertheless, it should be used only with caution.

These poisonous effects are to be kept in view in the choice of the remedy to be employed for *local disinfection* in the living body, especially *in cases of operations and wounds;* the demand, which is certainly not perfectly attainable, must be made, viz., that the substance in question act as energetically as possible upon the living protoplasm in general, and therefore be a strong disinfectant, without to any great extent exercising in the more highly organised beings, especially man, any deleterious actions upon the muscles and nerves.

It is by remedies which answer these conditions that the desired *effect upon the point of application can be most easily evoked of the requisite strength, yet without injuring the organism as a whole.* It is true that in consequence of their actions upon the protoplasm, these substances are even poisonous when they get into the blood in large quantities; nevertheless, their employment may be regulated in such a manner that a sufficiently powerful disinfection follows at the point of application, without injurious quantities being absorbed; for at these spots the remedy is very concentrated, and consequently acts antiseptically, while, after the slow and gradual absorption, such a degree of dilution is brought about through its diffusion in the body that no noticeable action follows. A skilful manipulation allows, however, the employment of substances which, like phenol, act very energetically upon the nervous system, and which become readily absorbed.

In many cases the *hydrocarbons*, which are insoluble in water, and solid but yet *volatile* at the ordinary temperature, may deserve the preference, because their absorption results slowly and the excretion keeps pace with this. Consequently, even though they be not quite harmless, they may be applied to wounds in great excess. Upon this depends the importance of *napthalin*, lately recommended by Fischer. Other simple and substituted hydrocarbons with similar properties may be ranked with the latter. It would be desirable, remembering iodoform, to subject more especially the iodine substitution products to a methodical trial.

The preference which the disinfectants of the aromatic series in many cases deserve, as compared with the metallic salts, *e.g.*, zinc chloride, in the surgical treatment of wounds, consists in the fact that they bring about no destruction of tissue, at any rate not to any great extent.

They certainly destroy not only the putrefactive organisms and their germs, but also cause *death of the tissues* in the neighbourhood of the point of application. These are then thrown off, so that the effect is the same as in a genuine cauterisation of them. Nevertheless, this occurs in most cases only to a limited degree; even carbolic acid, which is violently caustic in the concentrated condition, in the dilute solutions which are generally employed, brings about no material destruction of the tissue.

In disinfection in the living body the *digestive tract* comes also into consideration. The cavity of the mouth and the stomach offer no special difficulties to the application of suitable, but not intensely poisonous, disinfectants of this class, *e.g.*, salicylic and benzoic acids; since *in the intestine* putrefactive processes take place, even under ordinary circumstances, so much the oftener is cause given for undertaking disinfection of it in morbid states. Only the slowly absorbable substances reach the *deeper parts of the intestinal canal;* hence the aromatic compounds made use of as antiseptics in this locality, must have the same properties as regards their solubility and absorbability in the stomach as the substances which answer as aperients and anthelmintics.

Among the better known remedies, the almost insoluble *thymol* is in this respect of importance; it has also lately been employed to kill a dangerous intestinal parasite, the *Anchylostoma duodenale.*

The glycerine ethers of the aromatic acids, which are analogous to the ordinary neutral fats, and perhaps also those of the phenols, deserve special consideration. Like the fats, they pass through the stomach unaltered, and then become gradually digested in the intestine. In this process the aromatic substance is set free and comes into action. After the administration of *benzoate of glycerine* to dogs, free benzoic acid occurs in the fæces, so that its influence extends to the whole intestinal canal.

Presumably connected with the general action upon protoplasm is the influence which many, possibly even all, aromatic compounds exercise upon *the temperature and metabolism in febrile diseases.* In regard to these actions, we may refer to what has been said thereupon under quinine. Salicylic acid, which has in this respect been most thoroughly investigated, causes in small doses a rise of temperature, just as quinine does. The excretion of nitrogen by the urine is also increased; on the other hand, a decrease of the latter and a fall of temperature results after large doses. Here, too, one must be reminded of the fact that in normal animals, especially rabbits, results obtained as regards the behaviour of the temperature and metabolism under the influence of antipyretics, are not of themselves to be taken as a measure for the determination of the usefulness of the substance at the bedside.

The fever temperature and the metabolism can be the more easily lowered by the use of such remedies, and without danger to the whole organism, the less these affect in their own peculiar way the nerves and muscles, more especially the sensitive cardiac muscle. When, however, this general action, which affects all the protoplasmic structures, is too strong, it brings about collapse. If this threatens to come on immediately, the employment of the remedy must either cease entirely, or only be proceeded with under the greatest caution

The determination of the special indications in the individual feverish conditions is a matter of medical experience.

Of the substances which have recently found employment as *antifebrile* remedies, we must mention more particularly *benzoic acid*, *salicylic acid*, *hydro-chinon*, *resorcin*, *thymol*, *chinolin*, and derivatives of the same, *oxy-hydro-methyl-chinolin* or *kairin*, and *antipyrin*. The latter are not active because of chinolin forming itself out of quinine under certain conditions, but because they belong to the aromatic, and more particularly to the chinolin series. If kairin, and antipyrin especially, should show itself in reality more effective than chinolin, we would have to do here with similar relationships to those which exist between benzol and phenol.

Balsam of Peru and *liquid storax* are used for destroying the itch insect. With these *petroleum* can be classed as regards this action, for it is used for the destruction of parasites; it consists of a mixture of hydrocarbons of the fatty series, and belongs pharmacologically to the alcohol group. The resins and balsams are also antiseptics.

3. THE TANNINS AS ASTRINGENTS.

Those aromatic compounds which are readily volatile at ordinary temperatures, especially the turpentines and those ethereal oils which mostly belong to the aromatic series, and, further, the camphors and many phenols, *cause a more or less intense irritation at the points of application;* carbolic acid even causing cauterisation. Moreover, many ethereal oils cause specific stimulations of the organs of smell and taste.

We have already on various occasions spoken of the utilisation of these local actions for therapeutic purposes. We consequently here confine ourselves to the consideration of the tannins, for they play an important part as astringents in therapeutics.

Those substances which are distributed widely through the vegetable kingdom, and are designated as *tannins*, in spite of many very essential chemical differences, agree with one another almost perfectly in the fact that they *form extraordinarily stable compounds* (*leather*) *with the gelatine-yielding constituents of the tissues*, as *well as precipitate albumens, gelatine, and other albuminoids*, from their solutions in the form of similar but less stable compounds.

In the case of the metallic salts, it has been more particularly shown that the alterations at the point of application, designated as *astringency*, depend upon the formation of similar compounds. As regards the tannins, there is nothing special to be added in regard to the nature of this action. It is only necessary once more to refer to the fact that in employing the tannins the action comes on in a very typical form, because here no bye-products of any kind come into question, as in the case of the metallic salts, and to the fact that in spite of this, *even those remedies evoke stimulation and cauterisation, especially on the mucous membranes*, if they be applied in excess. However beneficial it may be in many cases to drink wines containing tannin, the misuse of these may easily lead to catarrh of the stomach.

Since all the tannins form compounds with the nitrogenous constituents of the tissues, so in like manner they act as astringents, and can be employed in exactly the same way.

Tannin proper, or tannic acid from galls, comes into the market sufficiently pure, and is particularly suitable in those cases in which it can be applied immediately to the affected locality; hence it can be used with special advantage in lotions for the skin, and for the treatment of various mucous membranes.

Since tannin, taken in ordinary medicinal doses by the mouth, is very rapidly fixed by the albuminous substances which occur in the contents of the stomach, or on the mucous membrane of the latter, it cannot get into the intestine in an active form. There, probably, the albuminous compound is again decomposed by the alkalies, but in this case there cannot be any question of an astringent action, because the tannin is held by the alkali.

If in the treatment of intestinal catarrhs *tannic acid must be conveyed on into the intestine*, it is desirable to employ, instead of pure tannin, crude vegetable substances rich in tannic acid. To these belong the concentrated extracts of numerous plants, including the catechu, which has no advantage over kino, rhatany, the extracts of rhatany and of tormentilla root, and other similar preparations.

It can readily be perceived that out of these extracts the different kinds of tannic acid be only gradually elutriated, and consequently that they pass on more readily into the intestinal canal unaltered. But even in these cases it is more particularly the colloid, the gummy, the mucilaginous constituents of these preparations, which, in the manner already more than once described, impede the absorption of the tannin, and favour their transit into the intestine. Hence it is much to be recommended that the influence of the colloid substances be aided by taking the tannin-containing remedies with mucilaginous decoctions.

The *absorption* of the tannins can result only in the form of the alkaline compounds, or of dissolved albuminous compounds. An astringent action upon internal organs cannot be expected from these combinations.

After the taking of tannin by man and animals, there are found *in the urine* the usual decomposition products of the former, *i.e.*, *gallic and pyro-gallic acid* (Wöhler and Frerichs). Along with these, bodies also occur, which, like tannin, precipitate albumen and gelatine (Schultzen, Lewin).

Whether the latter substances are unaltered tannins, which are set free from their compounds with albumens and alkalies at that part of the kidneys where the acid urine is secreted, and whether they there cause an astringent action on these organs, has not been decided with certainty. Athough the possibility of such behaviour cannot be denied, there are no further facts which are suited to support such an assumption.

The tannins which, like ordinary tannin, yield pyro-gallol, and which form blue-black compounds with the salts of iron, are to be distinguished from those which yield pyro-catechin and green compounds with iron. As regards the practical use, it makes no difference whether the tannic acid contained in a drug belongs to one or other category.

Chrysarobin has been used recently in skin diseases, and seems to act simultaneously as a *caustic, astringent, and antiseptic.* When oxidized by exposure to the air it yields chrysophanic acid.

Galls, oak, willow, elm, and horse-chestnut barks, kino, dragon's blood, logwood, catechu, tormentilla root, the leaves of the bearberry, and walnut, &c. &c., all belong to this group.

CHAPTER VII.

DIGESTIVE FERMENTS AND FOOD STUFFS.

In feeding those who are suffering from disturbances of the functions of the stomach and intestine, one aims either at supplying very easily digested or already digested food, or at encouraging the digestion by administering digestive ferments.

The greater or less *digestibility of foods depends upon their composition and preparation.* As regards their composition, a great deal depends not only upon the nature of the individual constituents, but also upon the manner and means by which these are associated with each other. Fat and albumen are in themselves easily digestible; fatty meat, on the other hand, is rather hard to digest, because the fibres of the meat, when surrounded by the fatty globules, are less accessible to the digestive ferment in the stomach. The flesh of old animals with firm connective tissue is not so easily digested as that of young ones. In the former case the preparation must be carried out differently from that in the latter.

Dietetics concerns itself with the art of cooking for therapeutic purposes, and this in many countries is taught as a special subject, and puts the physician in a position to hit upon the correct choice and preparation of the food for each case upon rational principles.

Cod liver oil has no importance for nutrition beyond that of an ordinary digestible fat; the impurities contained in it, *e.g.*, the biliary constituents, are, to say the least, indifferent. It is, however, *very easily digested* (Berthé, Naumann), because a part of the fats in it are in the form of free fatty acids. If these reach the intestine they become at once saponified without the co operation of the pancreatic ferment, and they emulsify the remaining fat and favour its absorption (Buchheim). Consequently, under otherwise similar circumstances, by the use of cod liver oil far more fat is absorbed and made useful for nutrition than by the use of the ordinary fats which consist only of glycerides. Cod liver oil is consequently a remedy well adapted for supplying fat in sufficient quantity for the nutrition of patients with weak digestions. Probably cod liver oil could be replaced judiciously by an artificially prepared mixture of free pure oleic acid, with suitable quantities of glycerides (Buchheim).

Among the *carbohydrates* the varieties of sugar, especially grape sugar, are the ultimate product of digestion in the mouth and intestine; consequently we can, to start with, employ *cane or grape sugar as food*, if we have reason to believe that the digestion of starch is interfered with in consequence of morbid states. But it is a question whether feeding with pure sugar is judicious; for large quantities of it might act in the same way as concentrated saline solutions, and injure the mucous membrane of a sensitive stomach.

Moreover, we must consider that sugar at times ferments and decomposes in the intestinal canal, and that thereby injurious products are formed. Finally, as regards feeding with sugar, its absorption and transformation differ with respect to time from those cases where starch or starch-containing foods are employed. The digestion of the latter demands a certain time, and the sugar formed is thereby continually absorbed and transformed in the organism. The operations of the latter spread over a long time, while, when sugar is supplied, the absorption follows rapidly, and large quantities enter the blood at one time. How far this is in certain cases injurious for the nutrition cannot be determined; nevertheless, these conditions are not to be left out of consideration in nourishing the sick with carbohydrates. In addition to this, there is the fact that when starch is supplied the sugar formed continually disappears from the digestive canal, and becomes correspondingly less harmful in the above-mentioned sense.

If it be permissible to assume that *starch may in many cases be more suitable than sugar in nutrition with carbohydrates*, there remains still the question *whether all kinds of starch are equally fitted for the nourishment of the sick*, and as to this we can make no positive statement as yet. Still it always lies within the bounds of possibility that one kind is preferable to another. In special investigations of this question it would mainly depend upon whether one sort of starch is readily digested, or whether, in consequence of the presence of other colloid constituents, unabsorbable bye-products are formed, which in the way before described interfere with the absorption of the sugar formed. In the conversion of potato starch into sugar, it does in reality seem that such colloid bye-products develop in considerable quantities. It is these substances which prevent the ready crystallisation of potato starch-sugar, and it is these, rather than specially poisonous substances, which make the artificial wines fabricated by its help injurious.

Formerly the starch, from various Aroidaceæ and Cannaceæ, known under the name of *arrowroot*, was more frequently used and highly valued than at present, especially for the feeding of children. Perhaps also in this case practice has outrun theoretical knowledge, and has found in this carbohydrate, in the above sense, a more perfectly digestible starch than is usually present in our ordinary food.

Of already digested albumens the *peptones* have latterly been employed. The preparations in use always contain albuminous substances, and for this reason are nutritious.

It is customary also to administer *pepsin*, in order to encourage the digestion of the ordinary albuminous foods, when one has reason to believe that the gastric juice is secreted in too small quantity, or in an insufficiently active state. Even as regards this remedy no certain decision has been arrived at. The *pepsin* wine and other preparations which contain glycerine exercise by no means a favourable influence upon the stomach. Moreover, there is no well-founded reason for administering pepsin with wine; we may just as well give them along with each other.

Inspissated ox-gall, from which great results were expected as an aid in the digestion of fat, has not answered those expectations.

Finally, *Nestlé's Children's Meal* and *Liebig's Children's Soup* deserve to be mentioned as being easily digestible forms of nourishment. The former preparation consists of sugar, milk, and wheat meal, the starch of which has been turned into dextrine by means of superheated steam. The latter is prepared from wheat meal, milk, barley malt, and carbonate of soda.

CHAPTER VIII.

MECHANICAL AND PHYSICALLY ACTING REMEDIES.

1. Mechanical Remedies of various kinds, including Surgical Dressings.

Here are included such dissimilar substances as *Lycopodium*, *Silver Leaf*, *Talc*, *Plaster of Paris*, *Gutta Percha*, *Absorbent Cotton Wool*, *Surgical Fungus*, *&c.* These serve partly for preparing various forms of medicines, *e.g.*, pills and dusting powders, partly for preparing surgical bandages, and partly for other purposes.

The antiseptic dressings and other surgical adjuvants, amongst which we have the bath sponge (*Spongia marina*), have not been introduced into the pharmacopœia, because they are provided directly by the makers or special merchants, especially surgical instrument makers.

2. Plasters and their Constituents.

The plaster masses consist of adhesive mixtures of resins, fat, and lead soaps, and when used are spread on cloth or paper. It is usual to distinguish according to their purposes—

(1.) Sticking plasters.
(2.) Covering plasters.
(3.) Medicated plasters.

Sticking plasters are employed in surgery for uniting the edges of wounds, and for fixing dressings. They must be so made that they adhere well, that they can be readily detached, and that they do not excite any strong irritation of the skin. They are at present manufactured and brought into commerce ready spread on linen, and of such excellent quality that those prepared according to the prescriptions of the pharmacopœia cannot come into competition with them.

The *covering plasters* are in many cases simple protecting and covering substances for the skin, and must be quite inactive. For this purpose lead plaster is adapted, and with it white-lead plaster agrees as regards the absence of any irritant action. In many cases a certain amount of *stimulation of the tissues* is desired in order to favour the breaking down or dissolution of morbid tissues. Plasters are then chosen which consist of resins, or of a mixture of the latter with lead soap, and these contain, as stimulating constituents, the oil of turpentine, or other mostly volatile substances, such as camphor. These are popularly called *drawing plasters.* Among the covering plasters we may reckon *collodion.*

Of the medicated plasters, only those are nowadays employed which contain *cantharides* and other acrid substances. In this it is mainly a matter of the special method of applying the substances in question, which are for the purpose of exciting inflammation with vesication or suppuration. The plaster mass fixes the substance to the skin, and at the same time aids its passage to the cutis, seeing that it answers as a solvent for the grease of the skin, and also for the active principle of cantharadin.

Belladonna, opium, hemlock, and other such plasters, have in Germany passed out of use, and rightly too. It is true that a passage of alkaloids into the blood occurs even with this manner of application, yet there are no grounds for using such a method—a method which presents the greatest uncertainties where one desires the absorption of these substances for the purpose of exciting a general action. On the skin itself, there are only a few alkaloids (veratrine, aconitine) which produce any effects.

In Germany, even those plasters have quite justly been omitted which differ from the simple covering or adhesive plasters merely by the presence of aromatic or ill-smelling (asafœtida) and colouring constituents; for such constituents are perfectly useless for the purpose which the plaster has to fulfil.

3. Ointments and Fatty Oils.

The *ointments* made from fats and other similar substances have a soft butter-like consistency, and are used for smearing on the skin, either in order to make it sleek, or to provide a protective covering for tender spots which have lost their epidermis, or, finally, to fix medicaments to the skin, especially those which would not adhere to in any other form. Usually they are substances which are intended to act upon the skin itself, yet, as with grey ointment, the passage of the active constituent into the blood may be intended. The absorption of most substances readily takes place in this method of application, because the ointment mass dissolves the fatty covering of the skin, and renders the penetration of the substance into the skin follicles possible. The *medicated ointments* have been cited under their respective groups.

The liniments also may be reckoned among the locally acting medicated ointments.

4. POULTICES AND FOMENTATIONS.

Poultices are pultaceous masses containing substances which swell up in water. They are made especially out of oleaginous seeds. They are applied warm to inflamed portions of the skin, in order to bring about absorption, or else purulent disintegration of the products of inflammation.

It is here merely a matter of the *purest form of the action of heat*, in which the tissue does not dry up or expand; for neither the former nor the latter action can occur, seeing that on the one hand the moisture of the poultice prevents the evaporation from the skin, and on the other hand the substances which swell up under water hold the latter with sufficient firmness to prevent it penetrating into the tissues and *causing* these to swell up too. Dry heat would cause irritation in such cases, and warm water would injure the skin too much by the inbibition. The fat and oil in the poultices are useful, because by the help of these they remain uniformly warm for a longer time. The oleaginous linseed is most used for making poultices. In commerce, poultices are to be obtained consisting of sheets of paper covered on one side with a layer of *expansible* substances. The sheets are applied to the skin in the moist state, and are warmed by the body.

In the case of the *emollient herbs*, the gentle irritation evoked by the ethereal oils comes into action as an active factor along with the warmth.

For this purpose mallow leaves, hibiscus leaves, camomile, &c., are often employed.

Peat and mud baths can, to a certain extent, be considered as poultices applied to the whole surface of the skin.

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